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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 333/18, 333/28, 333/44, 409/04, A61K 31/38, 31/44

A1

(11) International Publication Number: WO 94/26731

(43) International Publication Date: 24 November 1994 (24.11.94)

(21) International Application Number: PCT/CA94/00264

(22) International Filing Date: 11 May 1994 (11.05.94)

(30) Priority Data:
061,354 13 May 1993 (13.05.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 061,354 (CIP)
Filed on 13 May 1993 (13.05.93)

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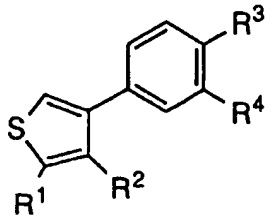
(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 2-SUBSTITUTED-3,4-DIARYLTHIOPHENE DERIVATIVES AS INHIBITORS OF CYCLOOXYGENASE

(57) Abstract

Disclosed are compounds of formula (I) useful in the treatment of cyclooxygenase mediated diseases such as pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries and Alzheimer's disease. R^3 is selected from the group consisting of (1) $-S(O)_2CH_3$, (2) $-S(O)(NH)CH_3$, (3) $-S(O)NH_2$, and (4) $-S(O)_2NH_2$.



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TITLE OF THE INVENTION

2-SUBSTITUTED-3,4-DIARYLTHIOPHENE DERIVATIVES AS INHIBITORS OF CYCLOOXYGENASE

BACKGROUND OF THE INVENTION

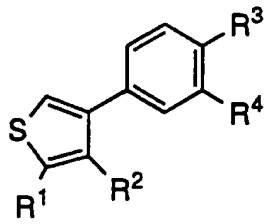
This invention relates to compounds and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases and methods of treatment thereof.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Up until recently, only one form of cyclooxygenase had been characterized, this corresponding to cyclooxygenase-1 or the constitutive enzyme, as originally identified in bovine seminal vesicles. Recently the gene for an inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has now also been cloned, sequenced and characterized from sheep, murine and human sources. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug (NSAID), and in

addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

SUMMARY OF THE INVENTION

The invention encompasses compounds of Formula I



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which are useful in the treatment of cyclooxygenase mediated diseases, in particular cyclooxygenase-2 mediated diseases.

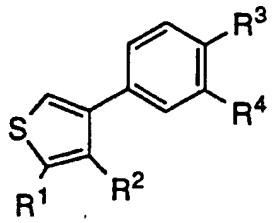
The invention also encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described herein.

The invention also encompasses methods of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula I



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and pharmaceutically acceptable salts thereof wherein:

R^1 is selected from the group consisting of

(a) hydrogen,
(b) halo, including fluoro, chloro, bromo and iodo,
(c) CN,
(d) NO_2,
(e) CF_3, and
(f) C_{1-6}alkyl;

R^2 is selected from the group consisting of

(a) C_{3-6}alkyl,
(b) mono or di substituted phenyl wherein the substitutents are selected from the group consisting of
  (1) hydrogen,
  (2) halo as defined above,
  (3) C_{1-6}alkoxy,
  (4) C_{1-6}alkylthio,
  (5) CN,
  (6) CF_3,
  (7) C_{1-6}alkyl, and
  (8) N_3,
(c) mono or di substituted heteroaryl wherein heteroaryl is
  (1) a monocyclic aromatic ring of 5 atoms, containing one hetero atom which is S, O or N and optionally 1, 2, or 3 additional hetero atoms which are N, or
  (2) a monocyclic aromatic ring of 6 atoms, containing 1, 2, 3, or 4 hetero atoms which are N, and

wherein the substitutents on the heteroaryl are selected from the group consisting of

(1) hydrogen,
(2) halo as defined above,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,

R^3 is selected from the group consisting of

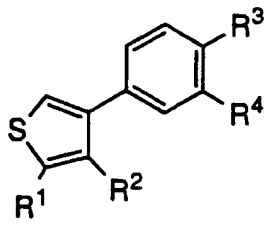
(1) $-S(O)_2CH_3$,
(2) $-S(O)(NH)CH_3$,
(3) $-S(O)NH_2$, and
(4) $-S(O)_2NH_2$;

R^4 is selected from the group consisting of

(1) hydrogen,
(2) halo as defined above,
(3) carboxy, and
(4) CF_3.

For purposes of this specification alkyl is defined to include linear, branched, and cyclic structures, with C_{1-6}alkyl including including methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C_{1-6}alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C_{1-6}alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

In one genus the invention encompasses compounds of Formula I



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and pharmaceutically acceptable salts thereof wherein:
R4 is hydrogen, and
R2 is selected from the group consisting of

(a) C3-6alkyl,
(b) mono or di substituted phenyl, and
(c) mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of
(1) furanyl,
(2) diazinyl, triazinyl, tetrazinyl,
(3) imidazolyl,
(4) isoxazolyl,
(5) isothiazolyl,
(6) oxadiazolyl,
(7) oxazolyl,
(8) pyrazolyl,
(9) pyrrolyl,
(10) thiadiazolyl,
(11) thiazolyl,
(12) thienyl,
(13) triazolyl,
(14) pyridyl, and
(15) tetrazolyl.

Exemplifying the invention are the compounds of Table 1 including:
3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)thiophene,

2-Nitro-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene,
2-Bromo-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene,
and
3-(4-Fluorophenyl)-4-(4-sulfamoylphenyl)thiophene.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases as disclosed herein comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

Within this embodiment the invention encompasses a method of inhibiting cyclooxygenase-2 and treating cyclooxygenase-2 mediated diseases as disclosed herein comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including

inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

As disclosed elsewhere in this specification in further detail, these diseases include pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries.

Compounds of Formula I are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns,

injuries, following surgical and dental procedures. In addition, such compounds may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compounds of Formula I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma and Alzheimers disease.

By virtue of their high cyclooxygenase-2 (COX-2) activity and/or their specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), compounds of Formula I will prove useful as alternatives to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, compounds of Formula I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-

sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising administration to a patient in need of such treatment a non-toxic therapeutically effective amount of compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. This activity is illustrated by their ability to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Accordingly, in one assay, the ability of the compounds of this invention to treat cyclooxygenase mediated diseases can be demonstrated by measuring the amount of prostaglandin E_2 (PGE_2) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a compound of Formula I. The IC50 values represent the concentration of inhibitor required to return PGE_2 synthesis to 50% of that obtained as compared to the uninhibited control. Illustrating this aspect, we have found that Compounds 1 through 25 are more than 100 times more effective in inhibiting COX-2 than they are at inhibiting COX-1. In addition they all have a COX-2 IC50 of 1 nM to 1 μM. By way of comparison, Ibuprofen has an IC50 for COX-2 of 1 μM, and Indomethacin has an IC50 for COX-2 of approximately 100 nM.

For the treatment of any of these cyclooxygenase mediated diseases compounds of Formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 gms per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 gms per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

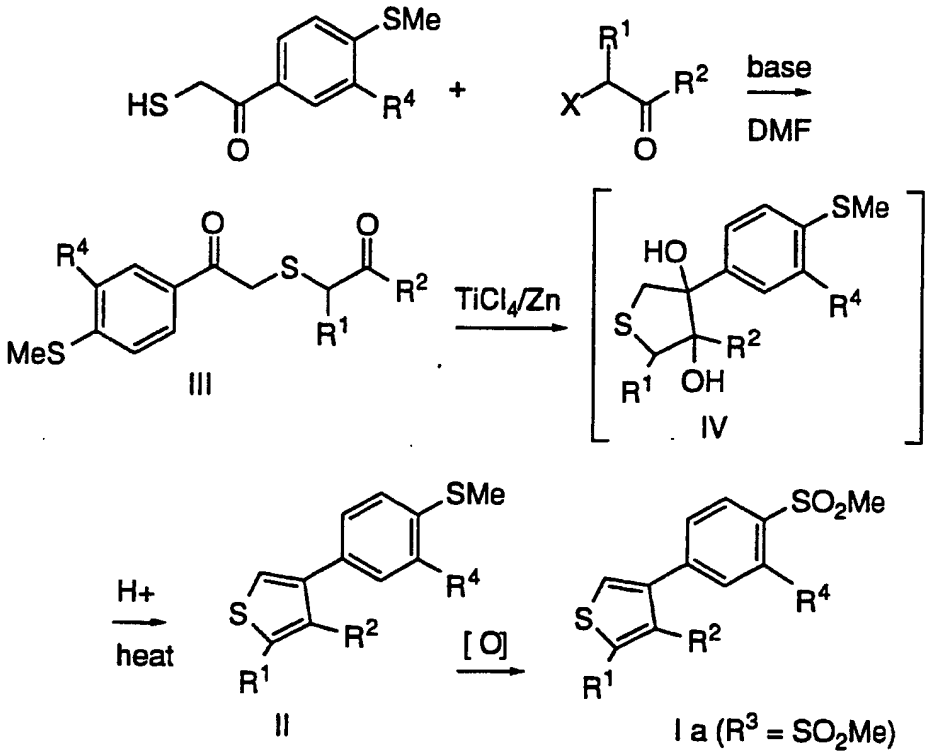
The compounds of the present invention are conviently prepared using the procedures described below.

Method A

The compounds of the present invention can be prepared by the general method described by J. Nakayama *et al.*, *Tetrahedron Lett.*,

26 (16), 1983-1984 (1985). Accordingly, intermediate **III**, obtained from the base catalyzed coupling of an α-mercaptoacetophenone and an α-haloacetophenone, is treated with titanium tetrachloride and zinc at low temperature in an inert solvent such as tetrahydrofuan to give an intermediate 3,4-dihydroxythiolane **IV**. This compound can then be dehydrated by heating it in a solvent such as toluene in the presence of an acid such as p-toluenesulfonic acid to yield **II**. This compound can be oxidized with a reagent such as the magnesium salt of mono-peroxyphtalic acid (MMPP) or m-chloroperoxybenzoic acid (mCPBA) to yield **I**.

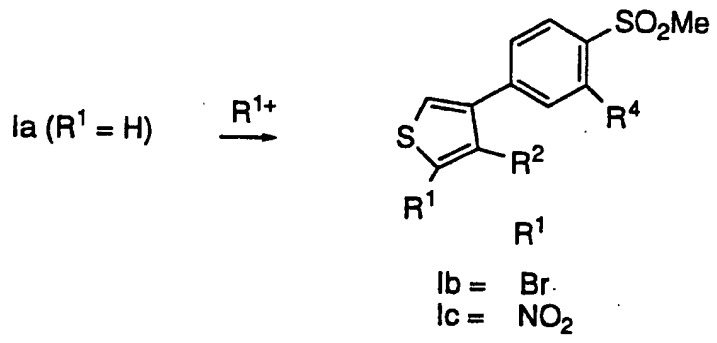
METHOD A



Method B

If I contains a substituent R1 which can be introduced by an aromatic electrophilic substitution, this can be carried out either on I or II. Accordingly, I can be treated with a halogenating agent such as bromine in a solvent such as glacial acetic acid to give the desired 2-bromothiophene (R1 = Br). When it is desired to have a nitrogen substituent at this position, for example R1 = NO_2, a cold mixture of I in a solvent such as acetic anhydride is treated with nitric acid to introduce the nitro group at the desired position.

METHOD B

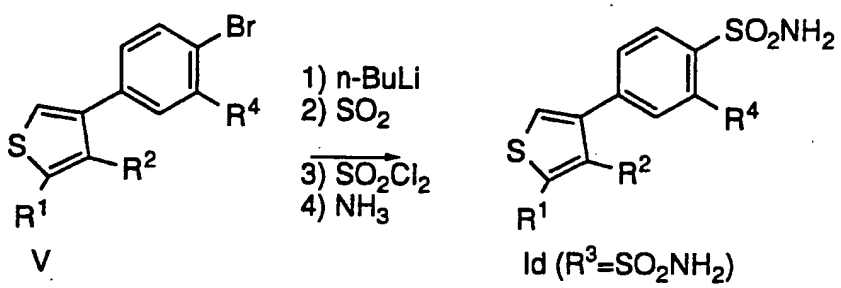


Ib = Br
Ic = NO_2

Method C

When R^3 is a sulfonamide group such as $R^3 = SO_2NH_2$, this substituent can be introduced by treating V with a base such as n-BuLi at low temperature and quenching the anion with sulfur dioxide to give a lithium arylsulfinate intermediate. This intermediate can then be converted to an arylsulfonyl chloride which will react with NH_3 to provide **Id**. This general procedure has been described by T. Hameda and O. Yonemitsu, Synthesis, 852 (1986).

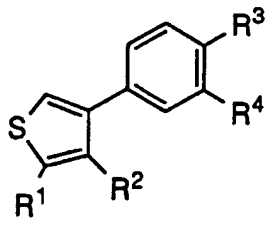
METHOD C



V Id (R^3=SO_2NH_2)

Table I illustrates compounds of Formula I, which are representative of the present invention. Representative biological data and the assays utilized to generate the data is provided immediately thereafter.

TABLE I



Compound	R1	R2	R3	R4
1	H	4-fluorophenyl	-S(O)2CH3	H
2	NO2	"	-S(O)2CH3	H
3	Br	"	-S(O)2CH3	H
4	H	"	-S(O)2NH2	H
5	F	"	-S(O)2CH3	H
6	Cl	"	-S(O)2CH3	H
7	I	"	-S(O)2CH3	H
8	CH3	cyclohexyl	-S(O)2CH3	H
9	CF3	4-fluorophenyl	-S(O)2CH3	H
10	CN	"	-S(O)2CH3	H
11	H	"	-S(O)(NH)CH3	H
12	H	2-pyridyl	-S(O)2CH3	H
13	H	2-thienyl	-S(O)2CH3	H
14	H	-n-pentyl	-S(O)2CH3	H
15	H	4-cyanophenyl	-S(O)2CH3	H
16	H	4-fluorophenyl	-S(O)2CH3	Br
17	H	4-fluorophenyl	-S(O)2CH3	CO2H

Whole Cell Cyclooxygenase Assays

Human osteosarcoma 143.98.2 cells were cultured in DULBECCOS MODIFIED EAGLES MEDIUM (SIGMA) containing 3.7 g/l $NaHCO_3$ (SIGMA), 100 µg/l gentamicin (GIBCO), 25 mM HEPES, pH 7.4 (SIGMA), 100 IU/ml penicillin (FLOW LABS), 100 µg/ml streptomycin (FLOW LABS), 2 mM glutamine (FLOW LABS) and 10% fetal bovine serum (GIBCO). Cells were maintained at 37°C, 6% CO_2 in 150 cm^2 tissue culture flasks (CORNING). For routine subculturing, media was removed from confluent cultures of cells, which were then incubated with 0.25% trypsin/0.1% EDTA (JRH BIOSCIENCES) and incubated at room temperature for approximately 5 minutes. The trypsin solution was then aspirated, and cells resuspended in fresh medium and dispensed at a ratio of 1:10 or 1:20 into new flasks.

U-937 cells (ATCC CRL 1593) were cultured in 89% RPMI-1640 (SIGMA), 10% fetal bovine serum (GIBCO), containing 50 IU/ml penicillin (FLOW LABS), 50 µg/ml streptomycin (FLOW LABS) and 2 g/l $NaHCO_3$ (SIGMA). Cells were maintained at a density of 0.1-2.0 x 10^6/ml in 1 liter spinner flasks (CORNING) at 37°C, 6% CO_2. For routine subculturing, cells were diluted in fresh medium and transferred to fresh flasks.

Assay Protocol

For cyclooxygenase assays, osteosarcoma 143.98.2 cells were cultured in 1 ml of media in 24-well multidishes (NUNCLON) until confluent. The number of cells per assay was determined from replicate plates prior to assays, using standard procedures. Immediately prior to cyclooxygenase assays, media was aspirated from cells, and the cells washed once with 2 ml of Hanks balanced salts solution (HBSS; SIGMA) prewarmed to 37°C. 1 ml of prewarmed HBSS was then added per well.

Immediatley prior to cyclooxygenase assays, the appropriate number of U-937 cells were removed from spinner cultures and centrifuged at 300 x g for 10 minutes. The supernatant was

decanted and cells washed in 50 ml of HBSS prewarmed to 37°C. Cells were again pelleted at 300 x g for 10 minutes and resuspended in prewarmed HBSS to a final cell density of approximately 1.5 x 10^6 cells/ml. 1 ml aliquots of cell suspension were transferred to 1.5 ml microcentrifuge tubes or 24-well multidishes (NUNCLON).

Following washing and resuspension of osteosarcoma 143 and U-937 cells in 1 ml of HBSS, 1 µl of test compounds or DMSO vehicle were added, and samples gently mixed. All assays were performed in triplicate. Samples were then incubated for 15 minutes at 37°C, prior to the addition of 10 µl of peroxide-free arachidonic acid (CAYMAN) diluted to 1 mM in HBSS. Control samples contained ethanol vehicle instead of arachidonic acid. Samples were again gently mixed and incubated for a further 10 minutes at 37°C. For osteosarcoma cells, reactions were then stopped by the addition of 100 µl of 1N HCl, with mixing, or by the rapid removal of media directly from cell monolayers. For U-937 cells, reactions in multiwell dishes or microcentrifuge tubes were stopped by the addition of 100 µl of 1N HCl, with mixing. Samples assayed in 24-multidishes were then transferred to microcentrifuge tubes. If necessary, samples were stored at 4°C prior to analysis of PGE_2 levels.

Quantitation of PGE_2 Concentrations

Osteosarcoma 143.98.2 and U-937 samples were neutralized by the addition of 100 µl of 1N NaOH. Samples were then mixed by vortexing, and PGE_2 levels measured using a PGE_2 radio-immunoassay (NEW ENGLAND NUCLEAR-DUPONT) according to the manufacturers instructions. This procedure was automated using a BIOMEK 1000 (BECKMAN). Levels of PGE_2 were calculated from the standard curve determined using BECKMAN IMMUNOFIT EIA/RIA analysis software.

Results

TABLE 2

Compound #	Drug Concentration nM	% Of Inhibition			
		Whole Cells		Microsomes	
		COX 2 (osteosarcoma)	COX 1 (U937)	COX 2 (osteosarcoma)	COX 1 (U937)
1	10	38	1		
	100	87	-2	98	15
2	10	27	0	20	5
	100	95	0	45	1
3	10	62	0	36	3
	100	84	0	81	-5
4	10	69	8	54	-5
	100	94	21	63	-8

EXAMPLES

The invention will now be illustrated by the following non-limiting examples. Unless stated otherwise: (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 me. Hg) with a bath temperature of up to 60°C; (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; (iv) melting points are uncorrected and `d' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in soee preparations; (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; (vi) yields are given for

illustration only; (vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; (viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)). Further, unless otherwise stated the following abbreviations have the indicated meanings:

DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
Et3N	=	triethylamine
MMMP	=	magnesium monoperoxyphthalate
Ph	=	phenyl
r.t.	=	room temperature
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl

Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

EXAMPLE 1 (Compound 1)

3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)thiophene

Step 1: 4'-(Methylthio)-2-chloroacetophenone

To a -5°C solution of thioanisole (26.4 g) and chloroacetyl chloride (27 g) in dichloromethane (600 mL) was added $AlCl_3$ (33.2 g) portion-wise. The mixture was allowed to warm up to 25°C and was stirred for 16 h. It was poured over ice water and stirred for 1.5 h. The mixture was extracted with CH_2Cl_2 (2 x 600 mL) and the combined extracts were washed with brine and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue swished in 1:25 ethyl acetate:hexanes. The solid was filtered and dried to yield 18 g of the title compound.

^1H NMR (CD_3COCD_3): δ 2.55 (3H, s), 4.95 (2H, s), 7.35-8.0 (4H, m).

Step 2: 4'-(Methylthio)-2-(acetylthio)acetophenone

To a 0°C suspension of 4'-(methylthio)-2-chloro-acetophenone (18 g) from Step 1 in THF (20 mL) and DMF (180 mL) was added potassium thioacetate (11.6 g). The mixture was warmed to 25°C and stirred 1.5 h. It was poured over ice/dilute $NaHCO_3$. The mixture was extracted with ethyl acetate:ether (2 x 200 mL) and the combined extracts were washed with H_2O, brine and dried with $MgSO_4$. After removal of the solvents *in vacuo*, the residue was

swished in 1:25 ethyl acetate:hexanes and the solid was filtered and dried to yield 18 g of the title compound.
^{1}H NMR (CD_3COCD_3): δ 2.35 (3H, s), 2.55 (3H, s), 4.45 (2H, s), 7.35-7.95 (4H, m).

Step 3: 4'-(Methylthio)phenacyl-4-fluorophenacyl sulfide

To a -5°C solution of 4'-(methylthio)-2-(acetylthio)-acetophenone (18 g) from Step 2 in THF (50 mL) and DMF (100 mL) was added hydrazine (2.6 mL). After 0.5 h Cs_2CO_3 (26 g) and 4-fluorophenacylchloride (21.6 g) were added and the mixture was poured over ice/dilute HCl. It was extracted with ethyl acetate (2 x 200 mL) and the combined extracts were washed with H_2O, brine and dried with $MgSO_4$. After removal of the solvents the residue was purified by chromatography to yield the title compound (12.76 g).
^{1}H NMR (CD_3COCD_3): δ 2.55 (3H, s), 4.05 (2H, s), 4.1 (2H, s), 7.2-8.2 (8H, m).

Step 4: 3-(4-Fluorophenyl)-4-((4-methylthio)phenyl)thiophene

To a -35°C solution of 4'-(methylthio)phenacyl-4-fluorophenacyl sulfide (8.8 g) from Step 3 in THF (225 mL) was added $TiCl_4$ (23.71 g) dropwise and the mixture was stirred for 0.5 h. Zinc powder (16.4 g) was added portionwise with vigourous stirring and the dark green suspension was stirred for 1 h at -35°C. The mixture was transferred via a canula to ice cold 1 M tartaric acid (1000 mL) and the mixture was stirred for 1 h. It was extracted with ethyl acetate (3 x 200 mL) and the combined extracts were washed with brine and dried with $MgSO_4$. After removal of the solvents the residue was dissolved in toluene (50 mL) containing p-TsOH (50 mg) and the mixture was refluxed for 3 h. The solvent was removed and the residue purified by chromatography to afford the title compound.
^{1}H NMR (CD_3COCD_3): δ 2.45 (3H, s), 7.0-7.5 (10H, m).

Step 5: 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)thiophene

To a 0°C suspension of 3-(4-fluorophenyl)-4-((4-methylthio)phenyl)thiophene (3 g) from Step 4 in MeOH and CH_2Cl_2 (50 mL) was added portionwise MMPP (6.8 g) and the mixture was allowed to react for 3 h while warming to 25°C. It was diluted with CH_2Cl_2 (50 mL) and filtered through celite. The filtrate was concentrated to dryness and purified by chromatography to yield the title compound (3.16 g).

^1H NMR (CD_3COCD_3): δ 3.05 (3H, s), 6.95-7.9 (10H, m).

EXAMPLE 2 (Compound 2)

2-Nitro-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene

To a 0°C suspension of 3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl) thiophene (1.32 g) from Example 1 in nitromethane (10 mL) and acetic anhydride (10 mL) was added 70% aqueous HNO_3 (320 µL). The cold bath was removed and the mixture was stirred 2 h at 25°C. It was then poured over ice H_2O and extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with brine, dried with $MgSO_4$ and the solvents were removed *in vacuo*. The residue was purified by chromatography to afford the title compound (858 mg).

Analysis calculated for $C_{17}H_{12}FNO_4S_2$:
C, 54.10; H, 3.21; N, 3.71.
Found: C, 53.77; H, 3.39; N, 3.62.

EXAMPLE 3 (Compound 3)

2-Bromo-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene

To a 0°C solution of 3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene (332 mg) from Example 1 in CH_2Cl_2 (2 mL) and acetic acid (2 mL) was added a 1 M solution of Br_2 in CCl_4 (1.1 mL) and the mixture was reacted for 2 h at 0°C. The mixture was then concentrated to dryness and the residue purified by chromatography to afford the title compound (203 mg).

Analysis calculated for $C_{17}H_{12}BrFS_2O_2$:
C, 49.65; H, 2.94.
Found: C, 49.83; H, 2.89.

EXAMPLE 4 (Compound 4)

3-(4-Fluorophenyl)-4-(4-sulfamoylphenyl)thiophene

Step 1: 3-(4-Fluorophenyl)-4-(4-bromophenyl)thiophene

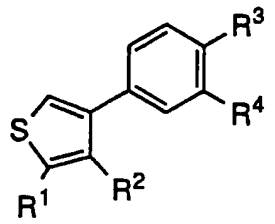
Following the procedures of Example 1, Steps 2-7, but replacing 4'-(methylthio)-2-chloroacetophenone by 4-bromophenyl bromide in Step 2, there was obtained the title compound.
^1H NMR (CD_3COCD_3): δ 7.0-7.3 (4H, m), 7.4-7.6 (6H, m)

Step 2: 3-(4-Fluorophenyl)-4-(4-sulfamoylphenyl)thiophene

To a -78°C solution of 3-(4-fluorophenyl)-4-(4-bromophenyl)thiophene (999 mg) in tetrahydrofuran (10 mL) was added 2.27 M n-BuLi (1.45 mL) and the mixture was stirred for 0.5 h at -78°C. It was then transferred dropwise into a -78°C solution of sulfur dioxide (10 mL) and tetrahydrofuran (10 mL) and the mixture was allowed to warm slowly to 25°C. The solvents were removed *in vacuo* and the solid obtained was suspended in hexanes (15 mL) and the suspension was cooled to 0°C. A 1 M dichloromethane solution of sulfuryl chloride (3 mL) was then added dropwise and the mixture was stirred for 0.5 h at 25°C. It was cooled again at 0°C and filtered. The solid obtained was taken into tetrahydrofuran and the mixture was cooled to 0°C before NH_3 was bubbled in for a few minutes. Removal of the solvents followed by purification on silica gel yielded the title compound (350 mg).
^1H NMR (CD_3COCD_3): δ 6.5-6.6 (2H, broad), 7.0-7.4 (6H, m), 7.55 (1H, d), 7.65 (1H, d), 7.75-7.8 (2H, d).

WHAT IS CLAIMED IS:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:

R1 is selected from the group consisting of

(a) hydrogen,
(b) halo, including fluoro, chloro, bromo and iodo,
(c) CN,
(d) NO_2,
(e) CF_3, and
(f) C_{1-6}alkyl;

R2 is selected from the group consisting of

(a) C_{3-6}alkyl,
(b) mono or di substituted phenyl wherein the substitutents are selected from the group consisting of
    (1) hydrogen,
    (2) halo as defined above,
    (3) C_{1-6}alkoxy,
    (4) C_{1-6}alkylthio,
    (5) CN,
    (6) CF_3,
    (7) C_{1-6}alkyl,
    (8) N_3,
(c) mono or di substituted heteroaryl wherein heteroaryl is

(1) a monocyclic aromatic ring of 5 atoms, containing one hetero atom which is S, O or N and optionally 1, 2, or 3 additional hetero atoms which are N, or

(2) a monocyclic aromatic ring of 6 atoms, containing 1, 2, 3, or 4 hetero atoms which are N, and

wherein the substitutents on the heteroaryl are selected from the group consisting of

(1) hydrogen,

(2) halo as defined above,

(3) C_{1-6}alkoxy,

(4) C_{1-6}alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6}alkyl,

(8) N_3;

R^3 is selected from the group consisting of

(1) $-S(O)_2CH_3$,

(2) $-S(O)(NH)CH_3$,

(3) $-S(O)NH_2$, and

(4) $-S(O)_2NH_2$;

R^4 is selected from the group consisting of

(1) hydrogen,

(2) halo as defined above,

(3) carboxy, and

(4) CF_3.

2. A compound according to Claim 1 wherein R^2 is selected from the group consisting of

(a) C_{3-6}alkyl,

(b) mono or di substituted phenyl, and

(c) mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,

(2) diazinyl, triazinyl, tetrazinyl,

(3) imidazolyl,
(4) isoxazolyl,
(5) isothiazolyl,
(6) oxadiazolyl,
(7) oxazolyl,
(8) pyrazolyl,
(9) pyrrolyl,
(10) thiadiazolyl,
(11) thiazolyl,
(12) thienyl,
(13) triazolyl,
(14) pyridyl, and
(15) tetrazolyl, and

wherein the substitutents on the phenyl or heteroaryl are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl, and
(8) N_3.

3. A compound according to Claim 2 wherein R^2 is selected from the group consisting of

(a) cyclohexyl, and
(b) mono or di substituted phenyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,

(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3;

R^4 is selected from the group consisting of
(1) hydrogen,
(2) halo as defined above, and
(3) carboxy.

4. A compound according to Claim 3 wherein
R^1 is selected from the group consisting of
(a) hydrogen,
(b) halo selected from the group consisting of fluoro, chloro and bromo,
(c) CN,
(d) C_{1-3}alkyl;
R^2 is selected from the group consisting of
(a) cyclohexyl, and
(b) mono or di substituted phenyl wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CN, and
(6) C_{1-3}alkyl;
R^4 is hydrogen.

5. A compound according to Claim 4 wherein
R^3 is selected from the group consisting of
(1) $-S(O)_2CH_3$,
(2) $-S(O)(NH)CH_3$, and
(3) $-S(O)NH_2$, and

(4) $-S(O)_2NH_2$.

6. A compound according to Claim 5 wherein R^1 is selected from the group consisting of

(a) hydrogen,

(b) halo selected from the group consisting of fluoro, chloro and bromo,

(c) CN, and

(d) C_{1-3}alkyl;

R^2 is selected from the group consisting of

(a) cyclohexyl, and

(b) mono substituted phenyl wherein the substitutents are selected from the group consisting of

(1) hydrogen,

(2) halo, selected from the group consisting of fluoro, chloro and bromo,

(3) C_{1-3}alkoxy,

(4) C_{1-3}alkylthio,

(5) CN, and

(6) C_{1-3}alkyl.

7. A compound according to Claim 2 wherein R^2 is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,

(2) diazinyl, triazinyl, tetrazinyl,

(3) imidazolyl,

(4) isoxazolyl,

(5) isothiazolyl,

(6) oxadiazolyl,

(7) oxazolyl,

(8) pyrazolyl,

(9) pyrrolyl,

(10) thiadiazolyl,

(11) thiazolyl,
(12) thienyl,
(13) triazolyl,
(14) pyridyl, and
(15) tetrazolyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,

R^4 is selected from the group consisting of

(1) hydrogen,
(2) halo as defined above,
(3) carboxy.

8. A compound according to Claim 7 wherein R^2 is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) 2-furanyl,
(2) 3-furanyl,
(3) 2-thienyl,
(4) 3-thienyl,
(5) 3-isoxazolyl,
(6) 4-isoxazolyl,
(7) 5-isoxazolyl,
(8) 3-isothiazolyl,
(9) 4-isothiazolyl,
(10) 5-isothiazolyl,
(11) 2-oxazolyl,

(12) 4-oxazolyl,
(13) 5-oxazolyl,
(14) 2-thiazolyl,
(15) 4-thiazolyl,
(16) 5-thiazolyl,
(17) 1,2,3-thiadiazol-4-yl,
(18) 1,2,3-thiadiazol-5-yl,
(19) 1,2,4-thiadiazol-3-yl,
(20) 1,2,4-thiadiazol-5-yl,
(21) 1,3,4-thiadiazol-2-yl,
(22) 1,2,5-thiadiazol-3-yl,
(23) 1,2,3-oxadiazol-4-yl,
(24) 1,2,3-oxadiazol-5-yl,
(25) 1,2,4-oxadiazol-3-yl,
(26) 1,2,4-oxadiazol-5-yl,
(27) 1,3,4-oxadiazol-2-yl,
(28) 1,2,5-oxadiazol-3-yl,
(29) pyrazol-4-yl,
(30) pyrazol-5-yl,
(31) 1,2,3-triadiazol-4-yl,
(32) 1,2,3-triadiazol-5-yl,
(33) 1,2,4-triadiazol-3-yl,
(34) 1,2,4-triadiazol-5-yl,
(35) 1,2-diazinyl,
(36) 1,3-diazinyl,
(37) 1,4-diazinyl,
(38) 1,2,3,4-tetrazin-5-yl,
(39) 1,2,4,5-tetrazin-4-yl,
(40) 1,3,4,5-tetrazin-2-yl,and
(41) 1,2,3,5-tetrazin-4-yl.

9. A compound according to Claim 8 wherein the heteroaryl is selected from the group consisting of

(1) 3-isoxazolyl,

(2) 4-isoxazolyl,
(3) 5-isoxazolyl,
(4) 3-isothiazolyl,
(5) 4-isothiazolyl,
(6) 5-isothiazolyl,
(7) 2-oxazolyl,
(8) 4-oxazolyl,
(9) 5-oxazolyl,
(10) 2-thiazolyl,
(11) 4-thiazolyl,
(12) 5-thiazolyl,
(13) 1,2,3-thiadiazol-4-yl,
(14) 1,2,3-thiadiazol-5-yl,
(15) 1,2,4-thiadiazol-3-yl,
(16) 1,2,4-thiadiazol-5-yl,
(17) 1,3,4-thiadiazol-2-yl,
(18) 1,2,5-thiadiazol-3-yl,
(19) 1,2,3-oxadiazol-4-yl,
(20) 1,2,3-oxadiazol-5-yl,
(21) 1,2,4-oxadiazol-3-yl,
(22) 1,2,4-oxadiazol-5-yl,
(23) 1,3,4-oxadiazol-2-yl,
(24) 1,2,5-oxadiazol-3-yl,
(25) 1,2-diazinyl,
(26) 1,3-diazinyl, and
(27) 1,4-diazinyl.

10. A compound according to Claim 9 wherein the hetreoaryl is selected from the group consisting of
(1) 2-oxazolyl,
(2) 4-oxazolyl,
(3) 5-oxazolyl,
(4) 3-thiazolyl,
(5) 4-thiazolyl,

(6) 5-thiazolyl,
(7) 1,3,4-thiadiazol-2-yl,
(8) 1,2,5-thiadiazol-3-yl,
(9) 1,3,4-oxadiazol-2-yl,
(10) 1,2,5-oxadiazol-3-yl,
(11) 1,2-diazinyl,
(12) 1,3-diazinyl, and
(13) 1,4-diazinyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CN, and
(6) C_{1-3}alkyl.

11. A compound according to Claim 10 wherein the hetreoaryl is selected from the group consisting of

(1) 2-oxazolyl,
(2) 4-oxazolyl,
(3) 5-oxazolyl,
(4) 2-thiazolyl,
(5) 4-thiazolyl,
(6) 5-thiazolyl,
(7) 1,3,4-thiadiazol-2-yl,
(8) 1,2,5-thiadiazol-3-yl,
(9) 1,3,4-oxadiazol-2-yl,
(10) 1,2,5-oxadiazol-3-yl,
(11) 1,2-diazinyl,
(12) 1,3-diazinyl, and
(13) 1,4-diazinyl.

12. A compound according to Claim 11 wherein
R^1 is selected from the group consisting of
(a) hydrogen,
(b) halo selected from the group consisting of fluoro, chloro and bromo,
(c) CN, and
(d) C_{1-3}alkyl;
R^4 is hydrogen.

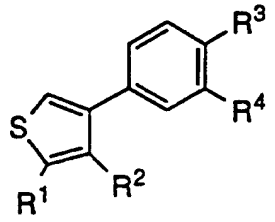
13. A compound according to Claim 11 wherein
R^3 is selected from the group consisting of
(1) $-S(O)_2CH_3$, and
(2) $-S(O)_2NH_2$;
R^4 is hydrogen.

14. A compound according to Claim 13 wherein
R^1 is selected from the group consisting of
(a) hydrogen,
(b) halo selected from the group consisting of fluoro, chloro and bromo,
(c) CN, and
(d) C_{1-3}alkyl;
R^2 is selected from the group consisting of
(1) 2-oxazolyl,
(2) 4-oxazolyl,
(3) 5-oxazolyl,
(4) 2-thiazolyl,
(5) 4-thiazolyl,
(6) 5-thiazolyl,
(7) 1,3,4-thiadiazol-2-yl,
(8) 1,2,5-thiadiazol-3-yl,
(9) 1,3,4-oxadiazol-2-yl,
(10) 1,2,5-oxadiazol-3-yl,
(11) 1,2-diazinyl,

(12) 1,3-diazinyl, and
(13) 1,4-diazinyl,
wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CN, and
(6) C_{1-3}alkyl;

R^4 is hydrogen.

15. A compound of Formula I wherein



R1	R2	R3	R4
H	4-fluorophenyl	-S(O)2CH3	H
NO2	"	-S(O)2CH3	H
Br	"	-S(O)2CH3	H
H	"	-S(O)2NH2	H
F	"	-S(O)2CH3	H
Cl	"	-S(O)2CH3	H
I	"	-S(O)2CH3	H
CH3	cyclohexyl	-S(O)2CH3	H
CF3	4-fluorophenyl	-S(O)2CH3	H
CN	"	-S(O)2H3	H
H	"	-S(O)(NH)CH3	H
H	2-pyridyl	-S(O)2CH3	H
H	2-thienyl	-S(O)2CH3	H
H	-n-pentyl	-S(O)2CH3	H
H	4-cyanophenyl	-S(O)2CH3	H
H	4-fluorophenyl	-S(O)2CH3	Br
H	4-fluorophenyl	-S(O)2CH3	CO2H

16. A pharmaceutical composition for inhibiting cyclooxygenase comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound or salt according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

17. A pharmaceutical composition for inhibiting cycloxygenase-2 comprising a pharmaceutically acceptable carrier and

a non-toxic therapeutically effective amount of compound or salt according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

18. A method of inhibiting cyclooxygenase comprising: administration to a patient in need of such inhibition of a non-toxic therapeutically effective amount of a compound according to Claim 1.

19. A method of inhibiting cyclooxygenase-2 comprising: administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1.

20. A pharmaceutical composition for the treatment of cyclooxygenase-2 mediated disease comprising a non-toxic therapeutically effective amount of compound according to Claim 1 and at least one or more ingredients selected from a pain reliever including acetaminophen or phenacetin; a potentiator including caffine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudopheorine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desocyephedrine; an antitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine.

21. A cyclooxygenase inhibitor pharmaceutical composition comprising an acceptable cyclooxygenase inhibiting amount of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

22. Use of a compound of formula (I) as defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cyclooxygenase mediated diseases.

23. A compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a pharmaceutically acceptable salt thereof for use in inhibiting cyclooxygenase.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 94/00264

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D333/18 C07D333/28 C07D333/44 C07D409/04 A61K31/38 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 087 629 (E.I. DU PONT DE NEMOURS & CO.) 7 September 1983 see page 8; claims	1,16
A	EP,A,0 365 089 (MERCK & CO., INC.) 25 April 1990 see claims	1,16
E	WO,A,94 15932 (G.D. SEARLE & CO.) 21 July 1994 see the whole document	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 1994	-5. 09. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA94/00264

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 and 19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/ composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA 94/00264

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0087629	07-09-83	AU-B-	553269	10-07-86
		AU-A-	1146083	08-09-83
		CA-A-	1242725	04-10-88
		JP-C-	1654086	13-04-92
		JP-B-	3014312	26-02-91
		JP-A-	58159489	21-09-83
		SU-A-	1250172	07-08-86
		US-A-	4590205	20-05-86
		US-A-	4820827	11-04-89
EP-A-0365089	25-04-90	JP-A-	2275875	09-11-90
WO-A-9415932	21-07-94	NONE		

Job Name:
US5466823.pdf

Job Owner Name:
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Time: 4:44:25 pm Date: 3-4-2004

US005466823A

United States Patent [19]

Talley et al.

[11] Patent Number: 5,466,823

[45] Date of Patent: Nov. 14, 1995

[54] **SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES**

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[21] Appl. No.: **160,594**

[22] Filed: **Nov. 30, 1993**

[51] **Int. Cl.**[6] **C07D 231/12**; C07D 413/10

[52] **U.S. Cl.** **548/377.1**; 544/140; 546/279; 548/364.1; 548/365.7

[58] **Field of Search** 548/377.1; 544/140

[56] **References Cited**

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5,134,142	7/1992	Matsuo et al. .	
5,134,155	7/1992	Connolly et al. .	
5,315,012	5/1994	Connolly et al. .	

FOREIGN PATENT DOCUMENTS

0347773	12/1989	European Pat. Off. .
0477049	3/1992	European Pat. Off. .

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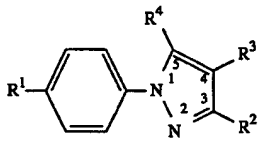
M. Hashem et al, *J. Med. Chem.*, 19, 229 (1976).
Maybridge Chemical Co./Ryan Scientific Catalog, Compound No. BTB 06812.
R. Soliman et al, J. Pharm. Sci., 76, 626 (1987).
H. Mokhtar, Pak. J. Sci. Ind. Res., 31, 762 (1988).
H. Mokhtar et al, Pak. J. Sci. Ind. Res., 34, 9 (1991).
M. Cocco et al, Il. Farmaco–Ed. Sci., 40, 272 (1985).
R. Soliman et al, J. Pharm. Sci., 72, 1004 (1983).
H. Feid–Allah, Pharmazie, 36, 754 (1981).
R. Soliman et al, J. Pharm. Sci., 70, 602 (1981).

Primary Examiner—Robert W. Ramsuer
Attorney, Agent, or Firm—Joseph W. Bulock; J. Timothy Keane

[57] **ABSTRACT**

A class of pyrazolyl benzenesulfonamide compounds is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by Formula I:



(I)

or a pharmaceutically-acceptable salt thereof.

13 Claims, No Drawings

SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES

FIELD OF THE INVENTION

This invention is in the field of anti-inflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Pyrazoles have been described for use in the treatment of inflammation. U.S. Pat. No. 5,134,142 to Matsuo et al describes 1,5-diaryl pyrazoles, and specifically, 1-(4-fluorophenyl)-5-[4 -(methylsulfonyl)phenyl]-3-trifluoromethyl pyrazole, as having anti-inflammatory activity.

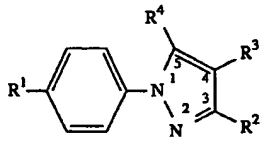
However pyrazolyl-benzenesulfonamides have not been described as having such activity. Certain substituted pyrazolyl-benzenesulfonamides have been described in the literature as synthetic intermediates. Specifically, 4-[5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound as an intermediate for compounds having hypoglycemic activity [R. Soliman et al, *J. Pharm. Sci.*, 76, 626 (1987)]. 4-[5-[2-(4-Bromophenyl)-2H-1,2,3 -triazol-4-yl]-3-methyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound and described as potentially having hypoglycemic activity [H. Mokhtar, *Pak. J. Sci. Ind. Res.*, 31, 762 (1988)]. Similarly, 4-[4-bromo-5-[2-(4-chlorophenyl)-2H-1,2,3 -triazol-4-yl]-3-methyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared [H. Mokhtar et al, *Pak. J. Sci. Ind. Res.*, 34, 9 (1991)].

The phytotoxicity of pyrazole derivatives is described [M. Cocco et al, *Il. Farmaco-Ed, Sci.*, 40, 272 (1985)], specifically for 1-[4-(aminosulfonyl)phenyl]-5 -phenyl-1H-pyrazole-3,4-dicarboxylic acid.

The use of 4-[3,4,5-trisubstituted-pyrazol-1 -yl]benzenesulfonamides as intermediates for sulfonylurea anti-diabetes agents is described, and specifically, 1 -[4-(aminosulfonyl)phenyl]-3-methyl-5-phenyl-1H-pyrazole-4-carboxylic acid [R. Soliman et al, *J. Pharm. Sci.*, 72, 1004 (1983)]. A series of 4-[3-substituted methyl-5 -phenyl-1H-pyrazol-1-yl]benzenesulfonamides has been prepared as intermediates for anti-diabetes agents, and more specifically, 4-[3-methyl-5-phenyl-1H-pyrazol-1 -yl]benzenesulfonamide [H. Feid-Allah, *Pharmazie*, 36, 754 (1981)]. In addition, 1-(4-[aminosulfonyl]phenyl)-5 -phenylpyrazole-3-carboxylic acid has been prepared from the above described 4-[3-methyl-5-phenyl-1H-pyrazol-1 -yl]benzenesulfonamide compound [R. Soliman et al, *J. Pharm. Sci.*, 70, 602 (1981)].

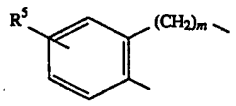
DESCRIPTION OF THE INVENTION

A class of compounds useful in treating inflammation-related disorders is defined by Formula I:



(I)

wherein R^1 is selected from sulfamyl, halo, alkyl, alkoxy, hydroxyl and haloalkyl; wherein R^2 is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl and heterocyclic; wherein R^3 is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl, heterocyclic, heterocycloalkyl and aralkyl; wherein R^4 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy hydroxyalkyl haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino; or wherein R^3 and R^4 together form



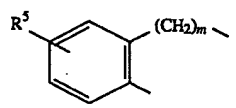
and m is 1 to 3, inclusive; and

wherein R^5 is one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, alkyl, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydrido, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, alkylamino, heterocyclic, nitro and acylamino; provided R^2 and R^3 are not identical radicals selected from hydrido, carboxyl and ethoxycarbonyl; further provided that R^2 cannot be carboxyl when R^3 is hydrido and when R^4 is phenyl; and further provided that R^4 is sulfamyl or N-alkylsulfamyl when R^1 is halo; or a pharmaceutically-acceptable salt thereof.

The phrase "further provided", as used in the above description, is intended to mean that the denoted proviso is not to be considered conjunctive with any of the other provisos.

Compounds of Formula I would be useful for the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid. arthritis, spondyloarthopathies, gouty arthritis, systemic lupus erythematosus, osteoarthritis and juvenile arthritis. Such compounds of Formula I would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as inflammatory bowel syndrome, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, hypersensitivity, conjunctivitis, gingivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects.

A preferred class of compounds consists of those compounds of Formula I wherein R^2 is selected from halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl and heterocyclic; wherein R^3 is hydrido; wherein R^4 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino; or wherein R^3 and R^4 together form



and m is 1 to 3, inclusive; and

wherein R^5 is one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, alkyl, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydrido, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, alkylamino, heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

A second preferred class of compounds consists of those compounds of Formula I wherein R^1 is sulfamyl; and wherein R^3 is hydrido; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is sulfamyl; wherein R^2 is selected from fluoro, chloro, bromo, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, nitro, formyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tertbutoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, amido, N-methylamido, N-ethylamido, N-isopropylamido, N-propylamido, N-butylamido, N-isobutylamido, N-tert-butylamido, N-pentylamido, N-cyclohexylamido, N-cyclopentylamido, N,N-dimethylamido, N-methyl-N-ethylamido, pyrrolidinoamido, piperidinoamido, N-phenylamido, N-(3-fluorophenyl)amido, N-(4-methylphenyl)amido, N-(3-chlorophenyl)amido, N-(4 -methoxyphenyl)amido, 2-pyridylamido, N-methyl-N-phenylamido, N-methyl-N-pyridylamido, methylsulfonyl, phenylsulfonyl, N-phenylsulfamyl, N-methylsulfamyl, N-ethylsulfamyl, N-isopropylsulfamyl, N,N-dimethylsulfamyl, N-methyl-N-ethylsulfamyl, N-methyl-N-(3 -chlorophenyl)sulfamyl, N-methyl-N-(2-pyridyl)sulfamyl, amidino, cyanoamidino, hydroxypropyl, hydroxymethyl, hydroxyethyl, carboxypropyl, carboxymethyl, carboxyethyl, tetrazolyl, imidazolyl and pyridyl; wherein R^3 is hydrido; wherein R^4 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 4-methylcyclohex-4-ene-1-yl, 1-cyclopentenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, cyano, carboxyl, amido, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tertbutoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, N-methylamido, N-ethylamido, N-isopropylamido, N-propylamido, N-butylamido, N-isobutylamido, N-tert-butylamido, N-pentylamido, N-cyclohexylamido, N-cyclopentylamido, N,N-dimethylamido, N-methyl-N-ethylamido, pyrrolidinoamido, piperidinoamido, N-phenylamido, N-(3-fluorophenyl)amido, N-(4-methylphenyl)amido, N-(3-chlorophenyl)amido, N-(4-methoxyphenyl)amido, 2-pyridylamido, N-methyl-N-phenylamido, N-methyl-N-pyridylamido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, trifluoromethoxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, sulfamyl, methylsulfamyl, amino, nitro, methylamino, dimethylamino, formylamino, acetamino, trifluoroacetamino and morpholino; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

4-[5-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

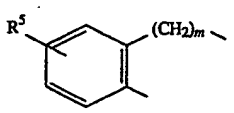
4-[5-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl] benzenesulfonamide;
4-[5-(4-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl] benzenesulfonamide;
4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-bromophenyl)-3-(cyano)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-nitrophenyl)-3-(cyano)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
1-[4-(aminosulfonyl)phenyl]-5-(4-bromophenyl)-1H-pyrazole- 3-carboxamide;
4-[5-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
methyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -aminophenyl)-1H-pyrazole-3-carboxylate;
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
ethyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole- 3-carboxylic acid;
4-[5-(2-pyrazinyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole- 3-carboxamide;
4-[5-(4-[methylthio]phenyl)-3-(difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(4-[methylsulfonyl]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,4-[difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,6-[difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-biphenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(2-pyrazinyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(5-chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(morpholino)phenyl)-3-difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(1-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(5-bromo-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-[trifluoromethyl]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-phenyl-3-(3-hydroxypropyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -fluorophenyl)-1H-pyrazole-3-carboxamide;
N-(4-methoxyphenyl)-1-[4-(aminosulfonyl)phenyl]-5 -(4-fluorophenyl)-1H-pyrazole-3-carboxamide;
N-(3-fluorophenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4 -fluorophenyl)-1H-pyrazole-3-carboxamide;
N-(3-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-(4-methylphenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H -pyrazole-3-carboxamide;
4-[5-(4-fluorophenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide;
1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-propanoic acid;
methyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -fluorophenyl)-1H-pyrazole-3-propanoate;
4-[5-(4-chlorophenyl)-3-(chloro)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(bromo)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(fluoro)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(fluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(chloromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(dichloromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
methyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
4-[5-(4-chlorophenyl)-3-(cyano)-1H-pyrazol-1 -yl]benzenesulfonamide;
N,N-dimethyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-methyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-methyl-N-ethyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-methyl-N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
4-[5-(4-chlorophenyl)-3-(dichlorofluoromethyl)-1H-pyrazol- 1-yl]benzene sulfonamide;
4-[5-(4-chlorophenyl)-3-(nitro)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(amidino)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(methylsulfonyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-methyl-aminosulfonyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(3,5-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,4,6-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,6-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,4,6-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3,5-dimethyl-4-methoxyphenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methoxy-3-methylphenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,4-dimethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3,4-dimethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3,4-dimethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(3,4-methylenedioxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluoro-2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-chloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chloro-2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-fluoro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluoro-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-chloro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chloro-2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3,4-dihydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(biphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(5-indanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(5-[2,3-dihydrobenzofuranyl])-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(6-[1,2,3,4-tetrahydronapthyl])-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-ethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-isopropylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(6-methoxy-2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(4-[N-methylamino]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-[N,N-dimethylamino]phenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-[N-formylamino]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-[N-acetylamino]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-[N-methylaminosulfonyl]phenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-hydroxymethylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(5-chloro-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-thiazolyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(2-oxazolyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(cyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(cyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(cycloheptyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(1-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(1-cyclopentenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-fluoro-2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chloro-3-methylphenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,5-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-ethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-n-butoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-[aminosulfonyl]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(6-methyl-3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-acetamidophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-[N-trifluoroacetamido]phenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(imidazolyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trichloromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(2-pyridyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzoic acid;

methyl-4-[1-[4-(aminosulfonyl)phenyl]-3 -(trifluoromethyl)-1H-pyrazol-5-yl]benzoate;
4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzamide;
1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazol- 1-yl]-3-propanoic acid;
ethyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
isopropyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
tert-butyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
propyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
butyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
isobutyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
pentyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
N-ethyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-isopropyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-propyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-butyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-isobutyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-tert-butyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole -3-carboxamide;
N-pentyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-cyclohexyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-cyclopentyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
4-[5-(4-chlorophenyl)-3-(pyrrolidinocarboxamide)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(piperidinocarboxamide)-1H-pyrazol- 1-yl]benzenesulfonamide;
N-(3-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-(2-pyridyl)-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide;
N-methyl-N-(3-chlorophenyl)-1-[4 -(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3 -carboxamide;
4-[5-(4-chlorophenyl)-3-(1,1-difluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(1,1-difluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(1,1-dichloroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(1,1-dichloropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-cyanoamidino)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(tetrazolyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(phenylsufonyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-phenylaminosulfonyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N,N-dimethylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-methyl-N-phenylaminosulfonyl)- 1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-ethylaminosulfonyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-isopropylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-methyl-N-ethylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-methyl-N-(3-chlorophenyl)aminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(N-methyl-N-(2 -pyridyl)aminosulfonyl)-1H-pyrazol-1-1]benzenesulfonamide;
4-[5-(2,3-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,5-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,3,4-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(3,4,5-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,4,5-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,5,6-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,3,4,5-tetrafluorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,3,4,6-tetrafluorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,3,5,6-tetrafluorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(pentafluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,3,4-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(3,4,5-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,4,5-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,5,6-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,3,4,5-tetrachlorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,3,4,6-tetrachlorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,3,5,6-tetrachlorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(pentachlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-tertbutylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-isobutylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylcyclohex-4-ene-1-yl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(5-chloro-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; and
4-[5-(5-bromo-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

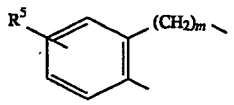
A third preferred class of compounds consists of those compounds of Formula I wherein R^1 is sulfamyl; wherein R^3 and R^4 together form



and m is 1 to 3, inclusive; and

wherein R^5 is one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, alkyl, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, alkylamino, heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is sulfamyl; wherein R^2 is selected from fluoro, chloro, bromo, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, nitro, formyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tertbutoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, amido, N-methylamido, N-ethylamido, N-isopropylamido, N-propylamido, N-butylamido, N-isobutylamido, N-tert-butylamido, N-pentylamido, N-cyclohexylamido, N-cyclopentylamido, N,N-dimethylamido, N-methyl-N-ethylamido, pyrrolidinoamido, piperidinoamido, N-phenylamido, N-(3-fluorophenyl)amido, N-(4-methylphenyl)amido, N-(3-chlorophenyl)amido, N-(4-methoxyphenyl)amido, 2-pyridylamido, N-methyl-N-phenylamido, N-methyl-N-pyridylamido, methylsulfonyl, phenylsulfonyl, N-phenylsulfamyl, N-methylsulfamyl, N-ethylsulfamyl, N-isopropylsulfamyl, N,N-dimethylsulfamyl, N-methyl-N-ethylsulfamyl, N-methyl-N-(3-chlorophenyl)sulfamyl, N-methyl-N-(2-pyridyl)sulfamyl, amidino, cyanoamidino, hydroxypropyl, hydroxymethyl, hydroxyethyl, carboxypropyl, carboxymethyl, carboxyethyl, tetrazolyl, imidazolyl and pyridyl; wherein R^3 and R^4 together form



and m is 1 to 3, inclusive;

and wherein R^5 is one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, cyano, carboxyl, amido, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tertbutoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, N-methylamido, N-ethylamido, N-isopropylamido, N-propylamido, N-butylamido, N-isobutylamido, N-tert-butylamido, N-pentylamido, N-cyclohexylamido, N-cyclopentylamido, N,N-dimethylamido, N-methyl-N-ethylamido, pyrrolidinoamido, piperidinoamido, N-phenylamido, N-(3-fluorophenyl)amido, N-(4-methylphenyl)amido, N-(3-chlorophenyl)amido, N-(4-methoxyphenyl)amido, 2-pyridylamido, N-methyl-N-phenylamido, N-methyl-N-pyridylamido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy n-butoxy, trifluoromethoxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, sulfamyl, methylsulfamyl, amino, nitro, methylamino, dimethylamino, formylamino, acetamino, trifluoroacetamino and morpholino; or a pharmaceutically-acceptable salt thereof.

A fourth preferred class of compounds consists of those compounds of Formula I wherein R^1 is selected from halo, alkyl, alkoxy, hydroxyl and haloalkyl; wherein R^2 is selected from haloalkyl; and wherein R^4 is phenyl substituted at a substitutable position with sulfamyl; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is selected from fluoro, chloro, bromo, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichloropropyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, methyl, ethyl, propyl, hydroxyl, methoxy, ethoxy, propoxy and n-butoxy; wherein R^2 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, difluoroethyl, dichlorofluoromethyl, difluoropropyl, dichloroethyl and dichloropropyl; and wherein R^3 is hydrido; or a pharmaceutically-acceptable salt thereof.

A specific compound of particular interest within Formula I is 4-[1-(4-fluorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a fifth preferred class of compounds which consists of compounds wherein R^1 is sulfamyl; wherein R^2 is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl and heterocyclic; wherein R^3 is selected from halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl, heterocyclic, heterocycloalkyl and aralkyl; wherein R^4 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkyltrio alkylsulfinyl alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

An even more preferred class contains compounds wherein R^2 is hydrido or haloalkyl; wherein R^3 is selected from alkyl, halo, carboxyalkyl, N-monoalkyl-N-hydroxyamido, N-monoalkyl-N-hydroxyamidoalkyl and N-monoalkylamido; and wherein R^4 is aryl optionally sub-

stituted at a substitutable position with halo; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consist of those compounds wherein R^1 is sulfamyl; wherein R^2 is selected from hydrido, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl; wherein R^3 is selected from fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, butyl, N-methylamido, N-ethylamido, N-isopropylamido, N-propylamido, N-butylamido, N-isobutylamido, N-tert-butylamido, N-pentylamido, N-cyclohexylamido, N-cyclopentylamido, carboxypropyl, carboxymethyl, carboxyethyl, N-methyl-N-hydroxyamido, N-methyl-N-hydroxyamidomethyl, N-methyl-N-hydroxyamidoethyl and N-methyl-N-hydroxyamidopropyl; and wherein R^4 is phenyl optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro and bromo; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest consists of compounds and their pharmaceutically acceptable salts thereof as follows

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-4-(methyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-4-fluoro-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-4-fluoro-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-4-(n-propyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-4-chloro-1H-pyrazol-1 -yl]benzenesulfonamide;

N-methyl-N-hydroxy-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-ethanamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-4 -(phenylethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-4-(2-[2 -pyridyl] ethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-4-([N,N-dimethylamino]ethyl)-1H-pyrazol-1-1]benzenesulfonamide;

4-[5-(4-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-3-chloro-1H-pyrazole-4-acetic acid;

1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-propanoic acid;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-propanoate;

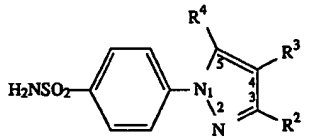
1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-3 -(trifluoromethyl)-1H-pyrazole-4-propanamide;

N-methyl-N-hydroxy-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-propanamide;

N-methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide; and

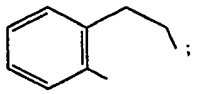
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-4-(methyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



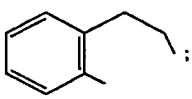
(II)

wherein R^2 is selected from hydrido haloalkyl, alkoxycarbonyl, cyano, amido, arylamido, carboxyalkyl and hydroxyalkyl; wherein R^3 is hydrido or halo; and wherein R^4 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfonyl, cyano, nitro, haloalkyl, alkyl, hydrido, alkoxy, haloalkoxy, sulfamyl, heterocyclic and amino; or wherein R^3 and R^4 together form



provided R^2 and R^3 are not both hydrido; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein R^2 is selected from hydrido, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tertbutoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, amido, N-phenylamido, N-(3-fluorophenyl)amido, N-(4-methylphenyl)amido, N-(3-chlorophenyl)amido, N-(4-methoxyphenyl)amido, 2-pyridylamido, hydroxypropyl, hydroxymethyl, hydroxyethyl, carboxypropyl, carboxymethyl and carboxyethyl; wherein R^3 is selected from hydrido, fluoro, chloro, iodo and bromo; wherein R^4 is selected from phenyl, biphenyl, pyrazinyl, cyclohexyl, cyclohexenyl and thienyl; and wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from chloro, bromo, fluoro, methylthio, methylsulfonyl, morpholinyl, amino, nitro, methyl, ethyl, propyl, isopropyl, butyl, methoxy, ethoxy, propoxy, butoxy, trifloromethoxy, trifluoroethoxy, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl; or wherein R^3 and R^4 together form



or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula II consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-4-chlororo-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl] benzenesulfonamide;
4-[5-(4-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl] benzenesulfonamide;
4-[5-phenyl-3-(trifluoromethyl-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-bromophenyl)-3-(cyano)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-nitrophenyl)-3-(cyano)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
1-[4-(aminosulfonyl)phenyl]-5-(4-bromophenyl)-1H-pyrazole- 3-carboxamide;
4-[5-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
methyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -aminophenyl)-1H-pyrazole-3-carboxylate;
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
ethyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxylate;
1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole- 3-carboxamide;
4-[5-(4-[methylthio]phenyl)-3-(difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(2,4-[difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,6-[difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-biphenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(5-chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;
4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
4-[5-(1-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;
4-[5-(5-bromo-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
4-[5-(4-[trifluoromethyl]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-phenyl-3-(3-hydroxypropyl)-1H-pyrazol-1 -yl]benzenesulfonamide;
N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-(4 -fluorophenyl)-1H-pyrazole-3-carboxamide;
N-[4-methoxyphenyl]-1-[4-(aminosulfonyl)phenyl]-5 -(4-fluorophenyl)-1H-pyrazole-3-carboxamide;
N-[3-fluorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4 -fluorophenyl)-1H-pyrazole-3-carboxamide;
N-[3-chlorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4 -fluorophenyl)-1H-pyrazole-3-carboxamide;
N-[4-methylphenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4 -fluorophenyl)-1H-pyrazole-3-carboxamide;
4-[4,5-dihydro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide; and
1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-propanoic acid.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (—CH_2—) radical. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro chloro or bromo to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy butoxy and trifluoromethoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals

such as phenyl, naphthyl, tetrahydronapthyl, indane and biphenyl. The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include pyrrolidyl and morpholinyl. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include thienyl, pyrryl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals —SO_2—. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide (—SO_2NH_2). The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes —CO_2H. The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes —(C=O)—. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3—(C=O)—. The term "alkylcarbonylalkyl", denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3CO$—C(=O)— and —(O=)C—OCH_3. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such "alkoxycarbonylalkyl" radicals include $(CH_3)_3COC(=O)(CH_2)_2$— and —$(CH_2)_2$(=O)$COCH_3$. The term "amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amine radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an —C(=NH)—NH_2 radical. The term "cyanoamidino" denotes an —C(=N—CN)—NH_2 radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cyclopropenyl, cyclobutenyl cyclopentenyl cyclohexenyl and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3—S—). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent —S(=O)— atom. The terms "N-alkylamino" and "N,N-dialkylamino" denote amine groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amine radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamine (CH_3C(=O)—NH—).

The present invention comprises a pharmaceutical composition for the treatment of inflammation and inflammation-associated disorders, such as arthritis, comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a therapeutic method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to a subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formula I.

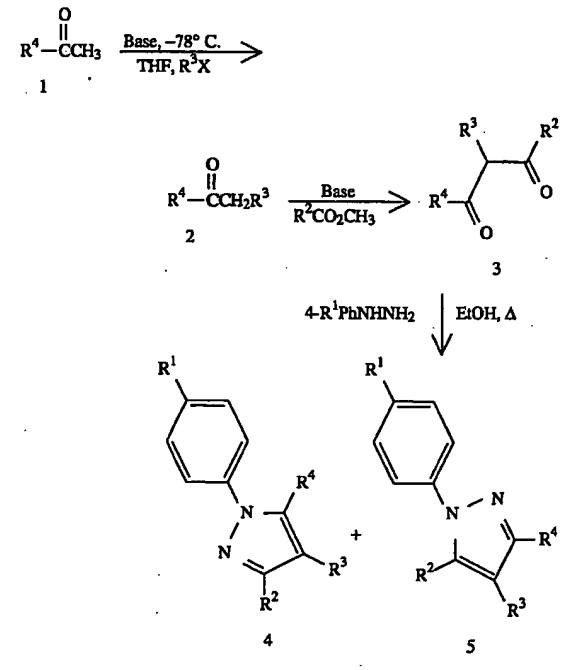
Also included in the family of compounds of Formula I are the Pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamolc), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, b-hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made

from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I–IV, wherein the R^1–R^5 substituents are as defined for Formula I, above, except where further noted. Synthetic Scheme I shows the preparation of tetrasubstituted pyrazoles from starting material 1. In step 1 of synthetic Scheme I, the phenyl-methyl ketone (1) is treated with a base (preferably a lithium base such as lithium diisopropylamide or LiHMDS) and an alkylating reagent (R^3X, where X represents a leaving group such as tosyl) to give the substituted ketone (2). In step 2, the substituted ketone (2) is treated with base, such as sodium methoxide, and an ester, or ester equivalent, to give the intermediate diketone (3) in a procedure similar to that developed by Reid and Calvin, *J. Amer. Chem. Soc.*, 72, 2948–2952 (1950). In step 3, the diketone (3) is reacted with a substituted phenylhydrazine in acetic acid or an alcoholic solvent to give a mixture of pyrazoles (4) and (5). Separation of the desired pyrazole (4) can be achieved by chromatography or recrystallization.

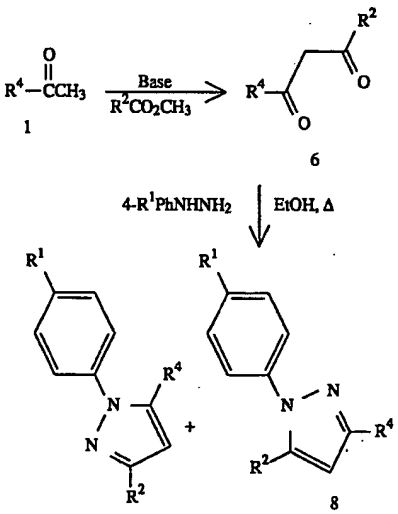
SCHEME I



Synthetic Scheme II shows the preparation of compounds embraced by Formula I where R^3 is a hydrogen atom. In step 1, ketone (1) is treated with a base, preferably NaOMe or NaH, and an ester, or ester equivalent, to form the intermediate diketone (6) which is used without further purification.

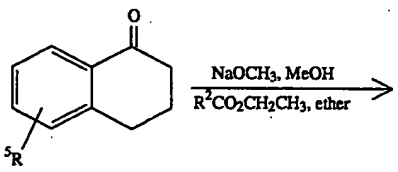
In step 2, diketone (6) in an anhydrous protic solvent such as absolute ethanol or acetic acid, is treated with the hydrochloride salt or the free base of a phenylhydrazine at reflux for 10 to 24 hours to afford a mixture of pyrazoles (7) and (8). Recrystallization from diethyl ether/hexane or chromatography affords (7), usually as a light yellow or tan solid.

SCHEME II

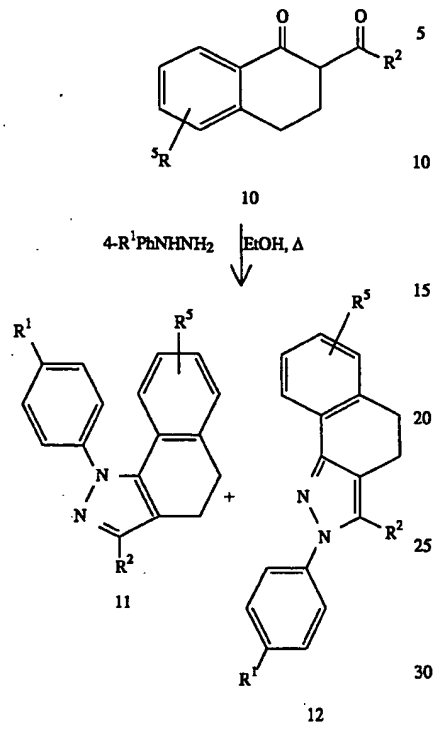


Synthetic Scheme III shows the procedure for preparation of 4,5-dihydrobenz[g]indazole compounds embraced by Formula I. In step 1, ethyl trifluoroacetate is reacted with base, such as 25% sodium methoxide in a protic solvent, such as methanol, and a 1-tetralone derivative (9) to give the intermediate diketone (10). In step 2, the diketone (10) in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the free base or hydrochloride salt of a phenylhydrazine at reflux for 24 hours to afford a mixture of pyrazoles (11) and (12). Recrystallization gives the 4,5-dihydro benz[g]indazolyl-benzenesulfonamide (11).

Scheme III

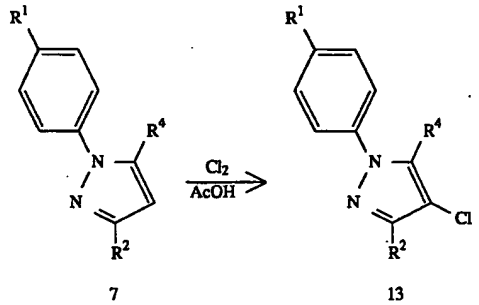


-continued
Scheme III



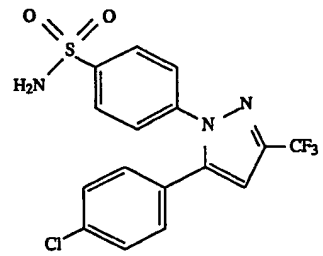
Synthetic Scheme IV shows the preparation of pyrazole compounds (13), where R^3 is chlorine, from the available pyrazole compounds (7), where R^3 is hydrogen. Chlorination results from passing a stream of chlorine gas at room temperature through a solution containing (7).

Scheme IV



The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I–II. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

EXAMPLE 1



4-[5-(4-Chlorophenyl)-3-trifluoromethyl)-1H-pyrazol-1yl]benzenesulfonamide

Step 1: Preparation of 4,4,4-trifluoro-1-[4 -(chloro)phenyl]-butane-1,3-diode

Ethyl trifluoroacetate (23.52 g, 166 mmol) was placed in a 500 mL three-necked round bottom flask, and dissolved in methyl tert-butyl ether (75 mL). To the stirred solution was added 25 weight % sodium methoxide (40 mL, 177 mmol) via an addition funnel over a 2 minute period. Next 4'-chloroacetophenone (23.21 g, 150 mmol) was dissolved in methyl tert-butyl ether (20 mL), and added to the reaction dropwise over 5 minutes. After stirring overnight (15.75 hours), 3N HCl (70 mL) was added. The organic layer was collected, washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a 35.09 g of yellow-orange solid. The solid was recrystallized from iso-octane to give 31.96 g, 85% of the dione, mp 66°–67° C.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide

4- Sulphonamidophenyl hydrazine hydrochloride (982 mg, 4.4 mmol 1.1 equivalent) was added to a stirred solution of 4,4,4-trifluoro-1-[4-(chloro)phenyl]-butane-1,3-dione (1.00 g, 4.0 mmol) in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. (HPLC area percent showed a 96:3 ratio of 4-[5-(4 -chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide to its regioisomer (4-[3-(4 -chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide). After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate and washed with water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo to give a light brown solid which was recrystallized from ethyl acetate and iso-octane to give the pyrazole 2, 1.28 g, 80% yield, mp 143°–145° C. HPLC showed that the purified material was a 99.5:0.5 mixture of 4-[5-(4-chlorophenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide to its regioisomer. ^1H NMR ($CDCl_3$/CD_3OD 10/1) d 5.2 (s, 2H), 6.8 (s, 1H), 7.16 (d, j=8.5 Hz, 2H), 7.35 (d, j=8.5 Hz, 2H), 7.44 (d, j=8.66, 2H), 7.91 (d, j=8.66, 2H); ^{13}C NMR ($CDCl_3$/CD_3OD 10/1) d 106.42 (d, j=0.03 Hz), 121.0 (q, j=276 Hz), 125.5, 1.26.9, 127.3, 129.2, 130.1, 135.7, 141.5, 143.0, 143.9 (q, j=37 Hz), 144.0; ^{19}F NMR ($CDCl_3$/CD_3OD 10/1) d –62.9. EI GC-MS M+=401.

The following compounds (Examples 1a to 1j) were obtained according to procedures similar to that exemplified in Example 1, with the substitution of the appropriate acetophenone.

(1a) 4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: off-white solid, mp 137°–139° C.; Anal. calc'd for $C_{16}H_{11}N_3O_2SBrF_3$: C, 43.07; H, 2.48; N, 9.42; Br 17.91 Found: C 43.01; H 2.32; N, 9.39; Br, 17.62.

(1b) 4-[5-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: yellow solid, mp 154°–155° C.; Anal. calc'd for $C_{16}H_{11}N_3O_2SClF_3$: C, 47.83; H, 2.76; N, 10.46; Cl, 8.82. Found: C, 47.61; H, 2.85; N, 10.31; Cl, 8.43.

(1c) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: yellow solid, mp 157°–159° C.; Anal. calc'd for $C_{17}H_{14}N_3O_2SF_3$: C, 53.54; H, 3.70; N, 11.02. Found: C, 53.17; H, 3.81; N, 10.90.

(1d) 4-[5-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: white solid, mp 159°–160° C.; Anal. calc'd for $C_{16}H_{11}N_3O_2SClF_3$: C, 47.83; H, 2.76; N, 10.46. Found: C, 47.47; H, 2.65; N, 10.31.

(1e) 4-[5-(4-trifluoromethylphenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: yellow solid, mp 144°–145° C.; Anal. calc'd for $C_{17}H_{11}N_3O_2SF_6$: C, 46.90; H, 2.55; N, 9.65. Found: C, 46.98; H, 2.57; N, 9.61.

(1f) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: mp 168°–169° C.; Anal. calc'd for $C_{16}H_{11}N_3O_2SF_4$: C, 49.87; H, 2.88; N, 10.90. Found: C, 49.83; H, 2.89; N, 10.86.

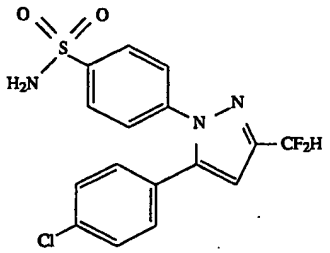
(1g) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide: mp 164°–165° C.; Anal. calc'd for $C_{16}H_{12}N_3O_2SF_3$: C, 52.31; H, 3.29; N, 11.43. Found: C, 52.14; H, 3.07; N, 11.34.

(1h) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: mp 153°–154° C.; Anal. calc'd for $C_{17}H_{14}N_3O_3SF_3$: C, 51.38; H, 3.55; N, 10.57. Found: C, 512.00; H, 3.48; N, 10.24.

(1i) 4-[5-(4-trifluoromethoxyphenyl)-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: white solid, mp 101°–103° C.; Anal. calc'd for $C_{17}H_{11}N_3O_3SF_6$: C, 45.24; H, 2.46; N, 9.31. Found: C, 45.22; H, 2.37; N; 9.29.

(1j) 4-[5-(2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide: white solid, mp 226°–128° C.; Anal. calc'd for $C_{17}H_{14}N_3O_2SF_3$: C, 53.54; H, 3.70; N, 11.02. Found: C, 53.52; H, 3.55; N, 11.06.

EXAMPLE 2



4-[5-(4-Chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

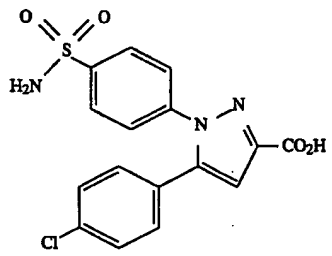
Step 1: Preparation of 4,4-difluoro-1-[4 -(chloro)phenyl]-butane-1,3-dione

Ethyl difluoroacetate (24.82 g, 200 mmol) was placed in a 500 mL three-necked round bottom flask, and dissolved in diethyl ether (200 mL). To the stirred solution was added 25 weight % sodium methoxide in methanol (48 mL, 210 mmol) via an addition funnel over a 2 minute period. Next, 4'-chloroacetophenone (25.94 g, 200 mmol) was dissolved in diethyl ether (50 mL), and added to the reaction dropwise over 5 minutes. After stirring overnight (18 hours), 1N HCl (250 mL) and ether (250 mL) were added. The organic layer was collected, washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give 46.3 g of a yellow solid. The solid was recrystallized from methylene chloride and iso-octane to give 31.96 g, 69% of the dione, mp 65°–66.5° C.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3 -(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

4-Sulphonamidophenyl hydrazine hydrochloride (1.45 g, 6.5 mmol 1.3 equivalent) and 4,4-difluoro-1-[4 -(chloro)phenyl]-butane-1,3-dione (1.16 g, 5 mmol) were dissolved in ethanol (10 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate (100 mL) and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give 1.97 g of a light brown solid which was recrystallized from ethanol and water to give 4-[5-(4 -chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide, 1.6 g, 83% yield, mp 185°–186° C.

EXAMPLE 3



4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate

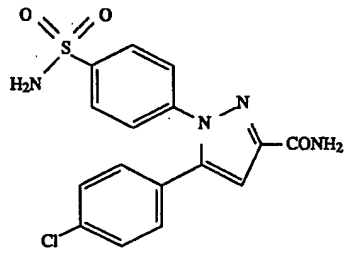
Step 1: Preparation of methyl-4-[4-(chloro)phenyl]-2,4-dioxobutanoate

Dimethyl oxalate (23.6 g, 200 mmol) was placed in a 500 mL three-necked round bottom flask, and dissolved in diethyl ether (200 mL). To the stirred solution was added 25 weight % sodium methoxide in methanol (48 mL, 210 mmol) via an addition funnel over a 2 minute period. Next, 4'-chloroacetophenone (25.94 g, 200 mmol) was dissolved in diethyl ether (50 mL), and added to the reaction dropwise over 3 minutes. After stirring overnight (18 hours), 1N HCl (400 mL) and ethyl acetate (750 mL) were added. The organic layer was collected, washed with brine (350 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give 45.7 g of a yellow solid. The solid was recrystallized from ethyl acetate and iso-octane to give 23 g, 48% of the dione, mp 108.5°–110.5° C.

Step 2: Preparation of 4-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl-1H-pyrazole-3-carboxylate

4-Sulphonamidophenyl hydrazine hydrochloride (1.45 g, 6.5 mmol 1.3 equivalent) and methyl-4-[4 -(chloro)phenyl] -2,4-dioxobutanoate (1.2 g, 5 mmol) were dissolved in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate (200 mL) and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give 1.7 g of a light brown solid which was recrystallized from methanol and water to yield 1.6 g, 85% of a white solid. This material was dissolved in methanol (150 mL) and 3N NaOH (75 mL) and stirred at reflux for 3 hours. The methanol was removed in vacuo and the aqueous solution acidified with concentrated HCl. The product was then extracted into ethyl acetate (200 mL) which was washed with brine (100 mL), dried over $MgSO_4$ filtered and concentrated to give 4-[4-(aminosulfonyl)phenyl] -5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate, 1.4 g, 74%, mp 135° C. (decomposed).

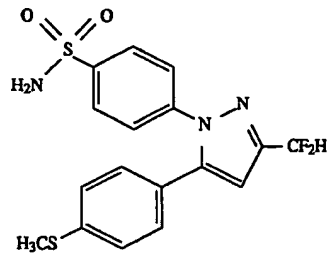
EXAMPLE 4



4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide

4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate (1.08 g, 2.86 mmol), HOBt (0.66 g, 4.3 mmol) and EDC (0.66 g, 3.4 mmol) were dissolved in dimethylformamide (DMF) (20 mL) and stirred at ambient temperature for 5 minutes. To this solution was added NH_4OH (30%, 2.9 mL) and the reaction stirred for an additional 18 hours. This solution was then poured into ethyl acetate (2.00 mL) and 1N HCl (200 mL), shaken and separated. The organic layer was washed with saturated $NaHCO_3$ (150 mL) and brine (15.0 mL), dried over $MgSO_4$, filtered and concentrated to yield 0.9 g of a white solid which was recrystallized from ethyl acetate and iso-octane to yield 4-[4-(aminosulfonyl)phenyl]-5-(4 -chlorophenyl)-1H-pyrazole-3-carboxamide, 0.85 g, 79%, mp 108°–110° C.

EXAMPLE 5



4-[5-(4-[Methylthio]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

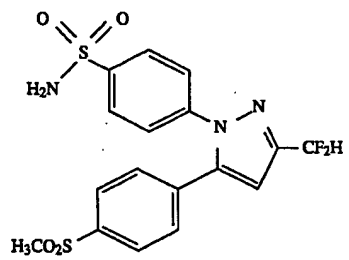
Step 1: Preparation of 4,4-difluoro-1-[4 -(methylthio)phenyl]-butane-1,3-dione

Ethyl difluoroacetate (7.4 g, 60 mmol) was placed in a 500 mL three-necked round bottom flask, and dissolved in diethyl ether (60 mL). To the stirred solution was added 25 weight % sodium methoxide in methanol (14.4 mL, 63 mmol) via an addition funnel over a 2 minute period. Next, 4'-methylthio acetophenone (9.97 g, 60 mmol) was dissolved in diethyl ether (20 mL), and added to the reaction dropwise over 5 minutes. After stirring overnight (16 hours), 1N HCl (150 mL) and ether (3.50 mL) were added. The organic layer was collected, washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give 13.4 g of a light-brown solid. The solid was recrystallized from ethanol and water to give 9.9 g, 68% of the dione, mp 68°–70° C.

Step 2: Preparation of 4-[5-(4-[methylthio]phenyl)-3-(difluoromethyl)-1H-pyrazol-1yl]benzenesulfonamide

4-Sulphonamidophenyl hydrazine hydrochloride (1.34 g, 6 mmol 1.2 equivalent) and 4,4-difluoro-1-[4 -(methylthio)phenyl]-butane-1,3-dione (1.22 g, 5 mmol) were dissolved in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate (200 mL) and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give 1.8 g of a light brown solid which was recrystallized from ethanol and water to yield 4-[5-(4 -methylthio]phenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide as a white solid 1.14 g, 58%, mp 157°–158° C.

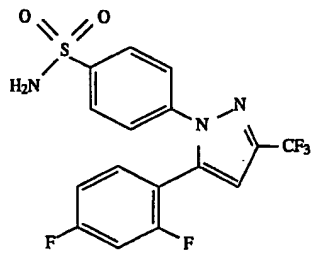
EXAMPLE 6



4-[5-(4-[Methylsulfonyl]phenyl)-3(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

4-[5-(4-[Methylthio]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (0.5 g, 1.27 mmol) was dissolved in methylene chloride (30 mL) and cooled to 0° C. To this solution was added m-chloroperoxybenzoic acid (MCPBA) (60%, 0.77 g, 2.7 mmol) and the solution was allowed to warm to room temperature while stirring for 18 hours. A solution of $Na_2S_2O_5$ (2 g) in H_2O (25 mL) was added to the reaction mixture and the solution stirred vigorously for 0.5 hour. The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated to yield 4-[5-(4-[methylsulfonyl]phenyl)-3 -(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide as a white solid, 0.22 g, 40%, mp=209°–210° C.

EXAMPLE 7



4-[5-(2,4-[Difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

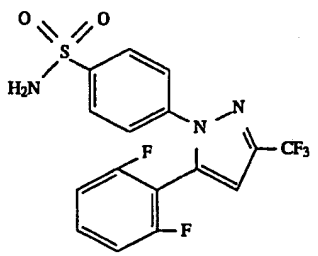
Step 1: Preparation of 4,4,4-trifluoro-1-[2,4 -(difluoro)phenyl]-butane-1,3-dione

Ethyl trifluoroacetate (2.19 g, 15 mmol) was placed in a 100 mL, round bottom flask, and dissolved in ether (10 mL). To the stirred solution was added 25 weight % sodium methoxide (3.35 g, 15 mmol) followed by 2',4'-difluoroacetophenone (2.11 g, 13 mmol). The reaction was stirred at room temperature overnight (15.8 hours), then poured into a separatory funnel and washed with 3N HCl (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil which solidified after cooling in dry ice. (2.67 g, 78%). ^1H NMR ($CDCl_3$) 300 MHz 15.00 (br s, 1H), 8.04 (m, 1H), 7.04 (m,1H), 6.95 (m,1H), 6.68 (s,1H) ^{19}F NMR ($CDCl_3$) 300 MHz: –76.88 (s), –99.93 (m), –103.92 (m) M+Li 259.

Step 2: Preparation of 4-[5-(2,4-[difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (2.31 g, 10.3 mmol) was added to a stirred solution of the diketone (2.37 g, 9.4 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred overnight (15.5 hours). After cooling to room temperature, the ethanol was removed in vacuo. The residue was dissolved in ethyl acetate, washed two times with water, washed two times with brine dried over $MgSO_4$ and concentrated in vacuo to give a brown foam which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a tan solid (1.94 g, mp 127°–30° C., 51%). ^1H NMR ($CDCl_3$) 300 MHz 7.91 (d, J=8.7 Hz, 2H), 7.45 (d, J=8.5 Hz, 2H), 7.28 (m,1H), 6.96 (m,1H), 6.87 (m,1H), 6.81 (s, 1H) 5.03 (br s, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –62.87 (s), –105.60(m), –108.09(m) M+H 404.

EXAMPLE 8



4-[5-(2,6-[Difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

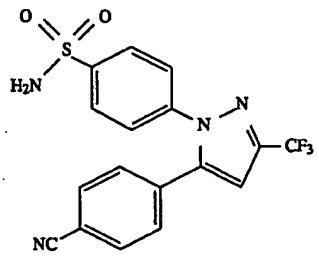
Step 1: Preparation of 4,4,4-trifluoro-1-[2,6 -(difluoro)phenyl]-butane-1,3-dione)

Ethyl trifluoroacetate (1.33 g, 9.3 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (10 mL). To the stirred solution was added 25 weight % sodium methoxide (2.11 g, 9.8 mmol) followed by 2',6' -difluoroacetophenone (1.32 g, 8.5 mmol). The reaction was stirred at room temperature overnight (15.8 hours), then poured into a separatory funnel and washed with 3N HCl (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give the diketone as a white solid (1.68 g, mp 40°–44° C., 79%). ^1H NMR ($CDCl_3$) 300 MHz 14.0 (br s, 1H), 7.49 (m, 1H), 7.02 (m, 2H), 6.36 (s, 1H); ^{19}F NMF ($CDCl_3$) 300 MHz: –76.78 (s), –109.77(s) M+H 253.

Step 2: Preparation of 4-[5-(2,6-[difluoro]phenyl)-3-trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (1.39 g, 6.2 mmol) was added to a stirred solution of the diketone (1.43 g, 5.7 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred overnight (15.75 hours. The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed two times with water, washed two times with brine, dried over $MgSO_4$, and concentrated in vacuo to give a brown solid (1.97 g) which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (1.00 g, mp 178°–80° C., 44%). ^1H NMR (acetone d^6) 300 MHz 7.97 (d, J=8.9 Hz, 2H), 7.62 (m,1H), 7.61 (d, J=8.9 Hz, 2H), 7.21 (s,1H), 7.16 (t, J=8.5 Hz, 2H), 6.75 (br s, 2H); ^{19}F NMR (acetone d^6) 300 MHz –63.26 (s), –112.17(s) M+H 404.

EXAMPLE 9



4-[5-(4-Cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

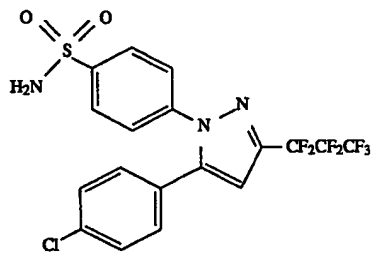
Step 1: Preparation of 4,4,4-trifluoro-1-[4-(cyano)phenyl]butane-1,3-dione

Ethyl trifluoroacetate (5.91 g, 41.6 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (30 mL). To the stirred solution was added 25 weight % sodium methoxide (9.02 g, 41.7 mmol) followed by 4-acetylbenzonitrile (5.46 g, 37.6 mmol). The reaction was stirred at room temperature for 4.2 hours, then treated with 1N HCl (50 mL). The reaction mixture was filtered to collect the diketone as a white solid (3.63 g). The filtrate was extracted with ethyl acetate, washed with brine (20 mL), dried over $MGSO_4$, and concentrated in vacuo, and recrystallized from methylene chloride to give an additionally 1.21 g (13%) of the diketone. (4.84 g, mp 124°–28° C. 53%). ^1H NMR ($CDCl_3$) 300 MHz 8.04 (d, J=8.5 Hz, 2H), 7.81 (d, J=8.5 Hz, 2H), 6.59 (s, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –77.12 (s); M+H 242.

Step 2: Preparation of 4-[5-(4-cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.57 g, 2.5 mmol) was added to a stirred solution of the diketone (0.54 g, 2.2 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 5.5 hours. The reaction mixture was filtered to remove the insoluble excess hydrazine and the ethanol was removed in vacuo. The residue was dissolved in ethyl acetate, washed two times with water, washed once with brine, dried over $MgSO_4$, and concentrated in vacuo to give a yellow solid which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a yellow solid (0.52 g, mp 196°–97.5° C., 59%). ^1H NMR ($CDCl_3$) 300 MHz 7.95 (d, J=8.8 Hz, 2H), 7.67 (d, J=8.5 Hz, 2H), 7.47 (d, J=8.8 Hz, 2H), 7.38 (d, J=8.5 Hz, 2H), 6.87 (s, 1H), 4.90 (br s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: –62.97 (s); M+H 393.

EXAMPLE 10



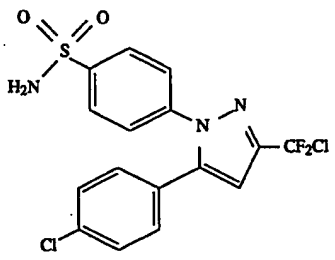
4-[5-(4-Chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide

Ethyl heptafluorobutyrate (5.23 g, 21.6 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (20 mL). To the stirred solution was added 25 weight % sodium methoxide (4.85 g, 22.4 mmol) followed by 4-chloroacetophenone (3.04 g, 19.7 mmol). The reaction was stirred at room temperature overnight (15.9 hours) and treated with 3N HCl (17 mL). The organic layer was collected washed with brine, dried over $MgSO_4$ concentrated in vacuo, and recrystallized from isooctane to give the diketone as a white solid (4.27 g, mp 27°–30° C., 62%). ^1H NMR ($CDCl_3$) 300 MHz 15.20 (br s, 1H), 7.89 (d, J=8.7 Hz, 2H), 7.51 (d, J=8.7 Hz, 2H), 6.58 (S, ^1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –80.94 (t), –121.01 (t), –127.17 (s); M+H 351.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (290 mg, 1.30 mmol) was added to a stirred solution of the diketone (400 mg, 1.14 mmol) in ethanol (5 mL). The reaction was heated to reflux and stirred overnight (23.8 hours). The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a white solid which was passed through a column of silica gel with ethyl acetate/hexane (40%) and recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (0.24 g, mp 168°–71° C., 42%). ^1H NMR ($CDCl_3$) 300 MHz 7.90 (d, J=8.7 Hz, 2H), 7.45 (d, J=8.7 Hz, 2H), 7.34 (d, J=8.5 Hz, 2H), 7.19 (d, J=8.5 Hz, 2H), 6.79 (s, 1H), 5.20 (br s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: –80.48 (t), –111.54 (t), –127.07 (s).

EXAMPLE 11



4-[5-(4-Chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

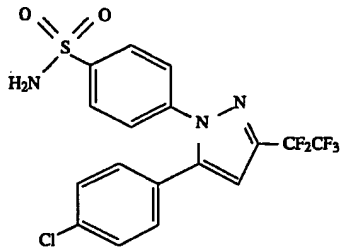
Step 1; Preparation of 4-chloro-4,4-difluoro-1-[4-(chloro)phenyl]butane-1,3-dione

Methyl 2-chloro-2,2-difluoroacetate (4.20 g, 29 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (10 mL). To the stirred solution was added 25 weight % sodium methoxide (6.37 g, 29 mmol) followed by 4'-chloroacetophenone (4.10 g, 26.5 mmol). The reaction was stirred at room temperature overnight (20.4 hours) then poured into a separatory funnel and washed with 3N HCl (15 mL), brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo and recrystallized from isooctane to give the diketone as a yellow solid (3.78 g, mp 53°–55° C., 53%). ^1H NMR ($CDCl_3$) 300 MHz 14.80 (br s, 1H), 7.87 (d, J=8.7 Hz, 2H), 7.50 (d, J=8.7 Hz, 2H), 6.49 (S, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –66.03 (s); M+267.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (1.39 g, 6.2 mmol) was added to a stirred solution of the diketone (1.43 g, 5.7 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred overnight (15.75 hours). The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a white solid which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (0.32 g, mp 130°–33° C., 41%). ^1H NMR ($CDCl_3$) 300 MHz 7.90 (d, J=8.9 Hz, 2H), 7.47 (d, J=8.7 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 7.19 (d, J=8.7 Hz, 2H), 6.76 (s, 1 H), 5.13 (br s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: –48.44 (s); M+417/419.

EXAMPLE 2



4-[5-(4-Chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide

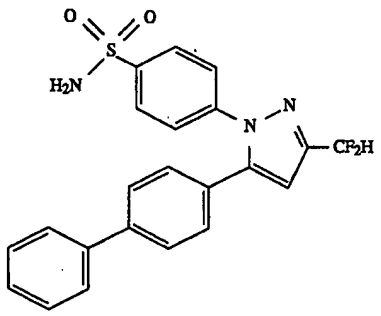
Step 1: Preparation of 4,4,5,5,5-pentafluoro-1-[4-(chloro)phenyl]-pentane-1,3-dione

Ethyl pentafluoropropionate (6.31 g, 32.8 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (15 mL). To the stirred solution was added 25 weight % sodium methoxide (7.90 g, 36.6 mmol) followed by 4'-chloroacetophenone (4.60 g, 29.8 mmol). The reaction was stirred at room temperature overnight (20.1 hours), then poured into a separatory funnel and washed with 3N HCl (20 mL), brine (20 mL), dried over $MGSO_4$, and concentrated in vacuo to give the diketone as a yellow powder which was recrystallized from isooctane to give yellow platelets. (7.07 g, mp 74°–77° C., 79%). ^1H NMR ($CDCl_3$) 300 MHz 15.20 (br s, 1H), 7.88 (d, J=8.9 Hz, 2H), 7.51 (d, J=8.9 Hz, 2H), 6.60 (S, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –82.97 (t,J=2.2 Hz), –124.23 (s); M+H 301.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (1.39 g, 6.2 mmol) was added to a stirred solution of the diketone (1.43 g, 5.7 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred overnight (15.75 hours). The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a white solid which was passed through a column of silica gel with ethyl acetate/hexane (16%) and recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (0.32 g, mp 145.5°–50° C., 40%). ^1H NMR ($CDCl_3$) 300 MHz 7.90 (d, J=8.9 Hz, 2H), 7.47 (d, J=8.7 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 7.19 (d, J=8.5 Hz, 2H), 6.79 (s, 1H), 5.18 (br s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: –84.66 (t), –113.70 (d).

EXAMPLE 13



4-[5-(4-Biphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4,4-difluoro-1-[4-biphenyl]-butane-1,3-dione)

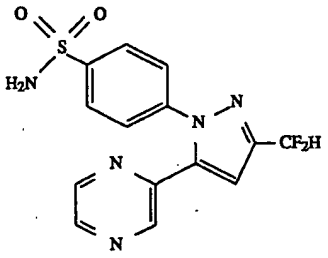
Ethyl trifluoroacetate (2.08 g, 16.8 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (5 mL). To the stirred solution was added 25 weight % sodium methoxide (3.73 g, 17.2 mmol) followed by 4-acetylbiphenyl (2.97 g, 15.1 mmol) and THF (10 mL). The reaction was stirred at room temperature overnight (16.4 hours), treated with 3N HCl (8 mL), and extracted with ethyl acetate. The organic layer was collected and washed with brine, dried over $MgSO_4$, concentrated in vacuo, and recrystallized from methylene chloride/isooctane to give the diketone as a brown solid (3.24 g, mp 115°–18° C., 78%). ^1H NMR ($CDCl_3$) 300 MHz 15.40 (br s, 1H), 8.01 (d, J=8.5 Hz, 2H), 7.74 (d, J=8.3 Hz, 2H), 7.63 (d, J=7.1 Hz, 2H), 7.49 (m, 3H), 6.61 (s, 1H), 6.02 (t, J=54.4 Hz,1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –126.91; M+274.

Step 2: Preparation of 4-[5-(4-biphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.40 g, 1.79 mmol) was added to a stirred solution of the diketone

(0.44 g, 1.60 mmol) in ethanol (5 mL). The reaction was heated to reflux and stirred overnight (23.6 hours). The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brown solid which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a brown solid (0.48 g, mp 167°–70° C., 70%) ^1H NMR ($CDCl_3$) 300 MHz 7.91 (d, J=8.7 Hz, 2H), 7.59 (d, J=8.3 Hz, 4H), 7.26–7.51 (m, 7H), 6.79 (s and t, J=54.9 Hz 2H), 4.89 (br s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: −112.72 (d); M+425.

EXAMPLE 14



4-[5-(4-Pyrazinyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

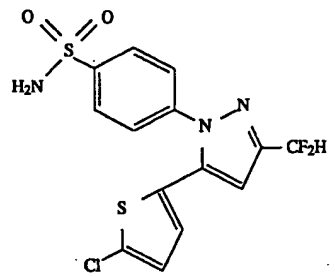
Step 1: Preparation of 4,4-difluoro-1-(2-pyrazinyl)-butane-1,3-dione

Ethyl difluoroacetate (2.23 g, 18 mmol) was placed in a 100 mL round bottom flask and dissolved in ether (10 mL). To the stirred solution was added 25 weight % sodium methoxide (4.68 g, 22 mmol) followed by acetylpyrazine (2.00 g, 16 mmol). After two hours stirring at room temperature, a precipitate formed and THF (10 mL) was added to the reaction. The reaction was stirred an additional 25.9 hours, then treated with 3N HCl (10 mL). The organic layer was collected, washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo and recrystallized from methylene chloride/isooctane to give the diketone as a brown solid (2.23 g, mp 103°–110° C., 68%). ^1H NMR ($CDCl_3$) 300 MHz 14.00 (br s, 1H), 9.31 (d, J=1.4 Hz, 1H), 8.76 (d, J=2.4 Hz, 1H), 8.68 (dd, J=1.4 Hz 2.4 Hz, 1H), 7.20 (s, 1H), 6.03 (t, J=54.0 Hz, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: −127.16 (d); M+200.

Step 2: Preparation of 4-[5-(2-pyrazinyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.37 g, 1.65 mmol) was added to a stirred suspension of the diketone (0.30 g, 1.50 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 5.3 hours. The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brown solid (0.36 g) which was recrystallized from ethyl acetate/ethanol/isooctane to give the pyrazole as a brown solid (0.20 g, mp 191°–94° C., 38%). ^1H NMR (acetone d^6) 300 MHz 8.94(d, J=1.4 Hz, 1H), 8.62 (d, J=2.4 Hz, 1H), 8.52 (dd, J=1.4 Hz 2.4 Hz, 1H), 7.95 (d, J=8.7 Hz, 2H), 7.61 (d, J=8.7 Hz, 2H), 7.30 (s, 1H), 7.02 (t, J=54.6 Hz, 1H), 6.73 (br s, 2 H); ^{19}F NMR (acetone d^6) 300 MHz: −113.67 (d); M+351.

EXAMPLE 15



4-[5-(5-Chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

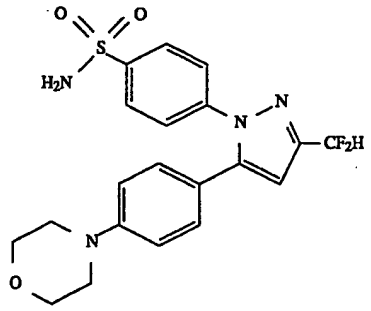
Step 1: Preparation of 4,4-difluoro-1-[5-chloro-2-thienyl]-butane-1,3-dione

Ethyl difluoroacetate (3.51 g, 28.3 mmol) was placed in a 100 mL round bottom flask and dissolved in ether (10 mL). To the stirred solution was added 25 weight % sodium methoxide (6.12 g, 28.3 mmol) followed by 2-acetyl-5-chlorothiophene (4.12 g, 25.6 mmol). A pink precipitate formed after 5 minutes which was dissolved by adding ether (10 mL) and THF (10 mL) to the reaction. The reaction was stirred at room temperature overnight (15.75 hours), then treated with 3N HCl (15 mL). The organic layer was collected and washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a red solid (5.94 g) which was recrystallized from methylene chloride/isooctane to give the like diketone as a yellow solid (2.02 g, mp 72°–77° C., 33%). ^1H NMR ($CDCl_3$) 300 MHz 14.60 (br s, 1H), 7.57 (d, J=4.2 Hz, 1H), 7.01 (d, J=4.2 Hz, 1H), 6.32 (s, 1H), 6.04 (t, J=54.2 Hz, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: −127.01 (d); M+238.

Step 2: Preparation of 4-[5-(5-chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.31 g, 1.39 mmol) was added to a stirred solution of the diketone (0.30 g, 1.26 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred 5.5 hours. The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a yellow solid (0.55 g) which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (0.38 g, mp 168°–70° C., 78%). ^1H NMR (acetone d^6) 300 MHz 8.03 (d, J=8.7 Hz, 2H), 7.70 (d J=8.7 Hz, 2H), 7.04 (m, 4H), 6.76 (br s, 2H) ; ^{19}F NMR (acetone d^6) 300 MHz: −113.71 (d); ^{13}C NMR (acetone d^6) 300 MHz 148.01(t), 144.69, 141.64, 137.70, 131.59, 128.90, 128.53, 127.48, 127.40, 126.47, 11.36(t), 105.89(t); M+389/391.

EXAMPLE 16



4-[5-(4-(Morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

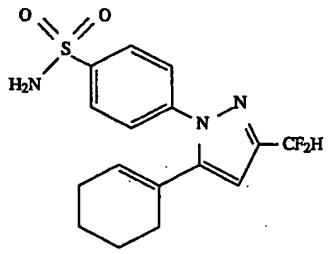
Step 1: Preparation of 4,4-difluoro-1-[4-(morpholino)phenyl]-butane-1,3-dione

Ethyl difluoroacetate (2.30 g, 18.5 mmol) was placed in a 100 mL round bottom flask and dissolved in THF (25 mL). To the stirred solution was added 25 weight % sodium methoxide (4.90 g, 22.6 mmol) followed by 4'-morpholinoacetophenone (3.45 g, 16.8 mmol). The reaction was stirred at room temperature overnight (15.8 hours), then treated with 3N HCl (13 mL). The reaction was extracted with ethyl acetate (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a green solid (4.36 g) which was recrystallized from methylene chloride/isooctane to give the diketone as a yellow solid (3.27 g, mp 102°–3° C., 69%). ^1H NMR ($CDCl_3$) 300 MHz 15.80 (br s, 1H), 7.86 (d, J=9.1 Hz, 2H), 6.90 (d, J=9.1 Hz 2H), 6.46 (s, 1H), 5.99 (t, J=54.4 Hz, 1H), 3.84 (m,4H), 3.36 (m, 4H); ^{19}F NMR ($CDCl_3$) 300 MHz: −126.75 (d); M+283.

Step 2: Preparation of 4-[5-(4-(morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.20 g, 0.89 mmol) was added to a boiling solution of the diketone (0.23 g, 0.81 mmol) in ethanol (5 mL). The reaction was stirred 5.0 hours. The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a yellow foam (0.36 g) which was recrystallized from methylene chloride/isooctane to give the pyrazole as a yellow solid (0.25 g, mp 167°–71° C., 71%). ^1H NMR ($CDCl_3$) 300 MHz 7.88 (d, J=8.7 Hz, 2H), 7.49 (d, J=8.9 Hz, 2H), 7.10 (d, J=8.9 Hz, 2H), 6.86 (d, J=9.1 Hz, 2H), 6.75 (t, J=55.0 Hz, 1H), 6,67 (s, 1H) 4.91 (br s, 2H), 3.86 (m, 4H), 3.21 (m, 4H); ^{19}F NMR ($CDCl_3$) 300 MHz: −112.67 (d); M+434.

EXAMPLE 17



4-[5-(1-Cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

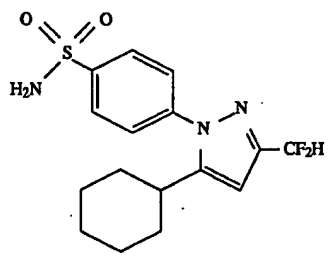
Step 1: Preparation of 4,4-difluoro-1-[2-cyclohexenyl]-butane-1,3-dione

Ethyl difluoroacetate (4.71 g; 38 mmol) was placed in a 100 mL round bottom flask and dissolved in ether (20 mL). To the stirred solution was added 25 weight % sodium methoxide (9.68 g, 45 mmol) followed by 1-acetyl-1-cyclohexene(4.27 g, 34 mmol). The reaction was stirred at room temperature overnight (17.5 hours), then treated with 3N HCl (20 mL). The organic layer was collected and washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brown oil (6.48 g, 93%). ^1H NMR ($CDCl_3$) 300 MHz 15.00 (br s, 1H), 6.09 (s, 1H), 5.92 (t, J=54.4 Hz,1H), 2.31 (m, 4H), 1.64 (m, 4H); ^{19}F NMR ($CDCl_3$) 300 MHz: −126.94; M+202.

Step 2: Preparation of 4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.71 g, 3.17 mmol) was added to a stirred solution of the diketone (0.58 g, 2.87 mmol) in ethanol (5 mL). The reaction was heated to reflux and stirred overnight (14.6 hours). The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water (35 mL), washed with brine (35 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brown oil which was passed through a column of silica gel with 16% ethyl acetate/hexane to isolate the pyrazole as a white solid (0.41 g, mp 1.60°–61° C., 40%) ^1H NMR ($CDCl_3$) 300 MHz 7.96 (d, J=8.5 Hz, 2H), 7.67 (d, J=8.6 Hz, 2H), 6.70 (t, J=55.0 Hz 1H), 6.50 (s, 1H), 5.90 (br s, 1H), 5.22 (br s, 2H), 2.02–2.11(m, 4H), 1.70–1.61 (m, 4H); ^{19}F NMR ($CDCl_3$) 300 MHz: −112.69 (d); M+353.

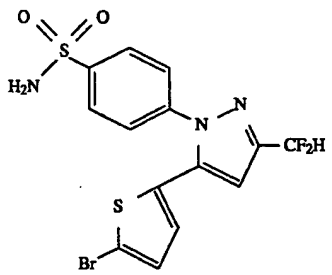
EXAMPLE 18



4-[5-(1-Cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-[5-(1-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (0.31 g, 0.88 mmol) was dissolved in ethanol (15 mL), 10% palladium on charcoal was added, and the suspension was stirred at room temperature under hydrogen (36 ps) for 18.25 hours. The reaction was filtered through celite, and the ethanol removed in vacuo to give a white solid, which was recrystallized from methylene chloride/isooctane (3.31 g, mp 199°–203° C., 99%). ^{1}H NMR (acetone d^6) 300 MHz 8.05 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.5 Hz, 2H), 6.69 (t, J=55.0 Hz 1H), 6.47 (s, 1H), 5.02 (br s, 2H), 2.67 (m, 1H), 1.71–1.88(m, 5H), 1.24–1.43 (m, 5H); ^{19}F NMR (acetone d^6) 300 MHz: –112.86 (d).

EXAMPLE 19



4-[5-(5-Bromo-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

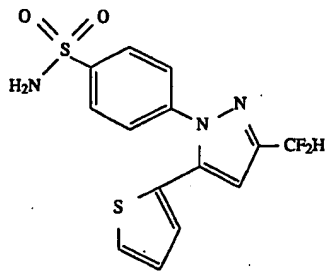
Step 1. Preparation of 4,4-difluoro-1-[5-bromo-2-thienyl]-butane-1,3-dione

Ethyl difluoroacetate (2.43 g, 19.6 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (15 mL). To the stirred solution was added 25 weight % sodium methoxide (4.23 g, 19.5 mmol) followed by 2 -acetyl-5-bromothiophene (3.59 g, 17.5 mmol). After two hours a precipitate formed and THF (15 mL) was added to allow stirring to continue. The reaction was stirred at room temperature 6.2 hours, then treated with 3N HCl (20 mL). The organic layer was collected and washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil which was crystallized from methylene chloride/isooctane to give yellow needles (3.63 g, mp 83.5°–85° C., 73%). ^{1}H NMR ($CDCl_3$) 300 MHz 14.60 (br s, 1H), 7.53 (d, J=4.0 Hz, 1H), 7.15 (d, J=4.0 Hz, 1H), 7.19 (m, 1H), 6.32 (s, 1H), 6.04 (t, J=54.2 Hz, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –127.00 (d) ; M+282.

Step 2. Preparation of 4-[5-(5-bromo-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.42 g, 1.88 mmol) was added to a stirred solution of the diketone (0.48 g, 1.70 mmol) in ethanol (5 mL). The reaction was heated to reflux and stirred overnight (17.25 hours). The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a white solid (0.67 g) which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (0.39 g, mp 168°–69° C., 53%). ^{1}H NMR (acetone d^6) 300 MHz 8.03 (d, J=8.5 Hz, 2H), 7.70 (d, J=8.7 Hz, 2H), 7.16 (d and part of CF_2H triplet, J=4.0 Hz 1.25H), 6.97 (m and part of CF_2H triplet, 2.5H) 6.78 (br s and part of CF_2H triplet, 2.25H); ^{19}F NMR (acetone d^6) 300 MHz: –113.70 (d); M+Li 440/442.

EXAMPLE 20



4-[5-(4-Thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

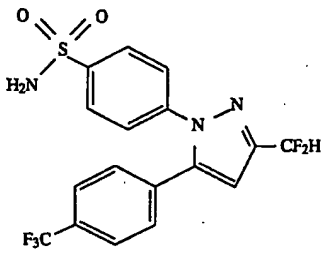
Step 1: Preparation of 4,4-difluoro-1-[2-thienyl]-butane-1,3-dione

Ethyl difluoroacetate (1.84 g, 14.8 mmol) was placed in a 100 mL round bottom flask and dissolved in ether (5 mL). To the stirred solution was added 25 weight % sodium methoxide (3.39 g, 15.7 mmol) followed by 2 -acetylthiophene (1.72 g, 13.6 mmol). The reaction was stirred at room temperature overnight (15.67 hours), then treated with 3N HCl (8 mL). The organic layer was collected and washed with brine, dried over $MgSO_4$, concentrated in vacuo, and recrystallized from methylene chloride/isooctane to give a brown solid (1.38 g, mp 78°–80° C., 50%). ^{1}H NMR ($CDCl_3$) 300 MHz 14.90 (br s, 1H), 7.80 (d, J=4.0 Hz, 1H), 7.71 (d, J=3.8 Hz, 1H), 7.19 (m, 1H), 6.41 (s, 1H), 6.04 (t, J=54.2 Hz, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: –126 98 (d); M+204.

Step 2: Preparation of 4-[5-(2-thienyl)-3-(difluoromethyl)-1H-pyrazo-1-yl]benzenesulfonamide

The 4-sulfonamidophenyl hydrazine hydrochloride (0.43 g, 1.92 mmol) was added to a stirred solution of the diketone (0.36 g, 1.76 mmol) in ethanol (5 mL). The reaction was heated to reflux and stirred overnight (17.67 hours). The ethanol was removed in vacuo and the residue was dissolved in ethyl acetate, washed with water (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brown solid which was recrystallized from ethyl acetate/isooctane to give the pyrazole as brown needles (0.30 g, top 190°–91° C., 48%). ^{1}H NMR (acetone d^6) 300 MHz 8.00 (d, J}8.2 Hz, 2H), 7.62 (m, 3H), 7.11 (m, and part of CF_2H triplet, 2.25H), 6.93 (s and part of CF_2H triplet, 1.5H), 6.76 (br s and part of CF_2H triplet, 2.25H); ^{19}F NMR (acetone d^6) 300 MHz: –113.60 (d); ^{13}C NMR (acetone d^6) 300 MHz 146.96(t), 144.43, 141.98, 138.84, 129.53, 129.02, 128.38, 127.86, 127.26, 126.36, 114.46(t), 105.57(t); M+Li 367.

EXAMPLE 21



4-[5-(4-[Trifluoromethyl]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

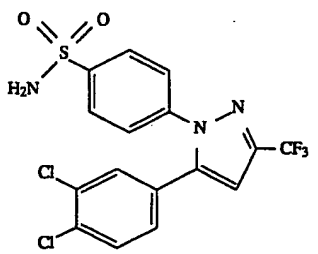
Step 1: Preparation of 4,4-difluoro-1-[4-(trifluoromethyl)phenyl]-butane-1,3-dione

Ethyl difluoroacetate (2.78 g, 22.4 mmol) was placed in a 100 mL round bottom flask and dissolved in ether (10 mL). To the stirred solution was added 25 weight % sodium methoxide (6.02 g, 27.8 mmol) followed by 4'-(trifluoromethyl)acetophenone (3.80 g, 20.2 mmol) and THF (20 mL). The reaction was stirred air room temperature overnight (15.6 hours), then treated with 3N HCl (20 mL). The organic layer was collected and washed with brine, dried over $MgSO_4$, concentrated in vacuo to give a brown oil (4.88 g, 91%). ^{1}H NMR (acetone d^6) 300 MHz 15.10 (br s, 1H), 8.03 (d, J=8.7 Hz, 2H), 7.77 (d, J=8.5 Hz, 2H), 6.59 (s, 1H), 6.02 (t, J=54.2 Hz, 1H); ^{19}F NMR (acetone d^6) 300 MHz: −63.70 (s), −127.10 (d); M+266.

Step 2: Preparation of 4-[5-(4-[trifluoromethyl]phenyl)-3-(difluoromethyl)-1H-pyrazol-1yl]benzenesulfonamide

The diketone (0.41 g, 1.54 mmol) was added to a stirred suspension of 4-sulfonamidophenyl hydrazine hydrochloride (0.39 g, 1.74 mmol) in ethanol (5 mL). The reaction was heated to reflux and stirred overnight (17.4 hours). The ethanol was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with water (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brown solid which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a tan solid (0.30 g, mp 202°–5° C., 46%). ^{1}H NMR (acetone d^6) 300 MHz 7.95 (d, J=8.9 Hz, 2H), 7.76 (d, J=8.2 Hz, 2H), 7.62 (d, J=8.1 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 7.03 (s, 1H), 6.99 (t, J=54.6 Hz, 1H), 6.73 (br s, 2H); ^{19}F NMR (acetone d^6) 300 MHz: −63.69 (s), −113.57 (d); M+H 418.

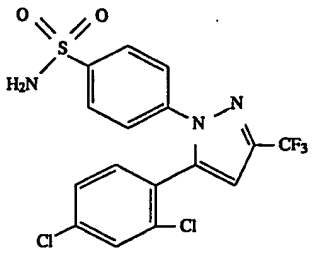
EXAMPLE 22



4-[5-(3,4-Dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

3,4-Dichloroacetophenone (6.24 g, 33 mmol) was dissolved in 25 mL methanol and 25% NaOMe in methanol (9 mL, 39.4 mmol) was added. The mixture was stirred at 25° C. for 5 minutes and ethyl trifluoroacetate (5 mL, 42 mmol) was added. The mixture was heated at 60° C. for 24 hours, cooled and the volume reduced by 50%. The mixture was poured into 100 mL of 10% HCl and extracted with four 75 mL portions of ethyl acetate. The combined extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude diketone as a brown gum (8.54 g, 30 mmol) which was used without further purification. The crude diketone (3.16 g, 11.1 mmol) and 4 -sulfonamidophenylhydrazine.HCl (3.31 g, 14.8 mmol) were dissolved in 75 mL of absolute ethanol and the mixture stirred at reflux for 24 hours. The mixture was cooled, filtered and concentrated in vacuo to afford the crude pyrazole. Recrystallization from diethyl ether/hexane afforded the pure pyrazole (2.43 g, 51%) as a yellow solid, mp 145°–147° C.; Anal. calc'd for $C_{16}H_{10}N_3O_2SCl_2F_3$: C, 44.05; H, 2.31; N, 9.63; Cl, 16.25. Found: C, 44.00; H, 2.20; N, 9.63; Cl, 16.46.

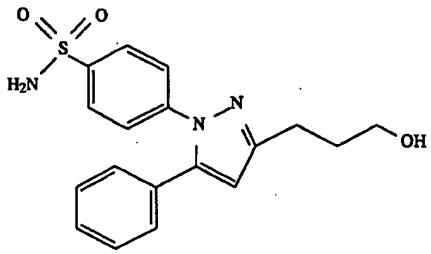
EXAMPLE 23



4-[5-(2,4-Dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Following the procedure of Example 22, but substituting 2,4-dichloroacetophenone for 3,4 -dichloroacetophenone afforded 4-[5-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide as a tan solid, mp 153°–155° C.; Anal. calc'd for $C_{16}H_{10}N_3O_2SCl_2F_3$—0.10 H_2O: C, 43.87; H, 2.35; N, 9.59. Found: C, 43.78; H, 2.13; N, 9.56.

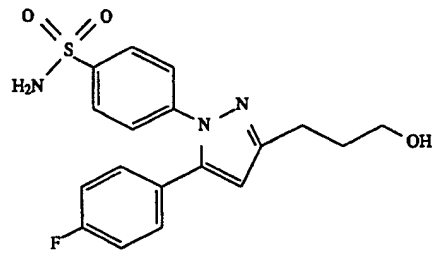
EXAMPLE 24



4-[5-Phenyl-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide

A 60 dispersion of sodium hydride in mineral oil (4.0 g, 100 mmol) was twice washed with hexane (100 mL each) and dried under a stream of nitrogen. Ether (300 mL) was added followed by dropwise addition of ethanol (0.25 mL) and γ-butyrolactone (4.0 mL, 52 mmol). The mixture was cooled to 10° C. and acetophenone (5.8 mL, 50 mmol) in ether (40 mL) was added dropwise over 1 hour. The mixture was warmed to 25° C. and stirred overnight. The mixture was cooled to 0° C. and quenched with ethanol (5 mL) followed by 10% aqueous ammonium sulfate (100 mL). The organic solution was separated, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with 1:hexane/ethyl acetate to give the desired diketone (3.4 g) as an oil. Pyridine (0.34 mL, 4.2 mmol) and the diketone (700 mg, 3.4 mmol) in methanol (3 mL) were added to a slurry of 4-sulfonamidophenylhydrazine-HCl (750 mg, 3.4 mmol) in methanol (8 mL). The mixture was stirred at 25° C. overnight and concentrated in vacuo. The residue was dissolved in methylene chloride and the solution washed with 1N HCl. The organic solution was separated, dried and concentrated. The residue was chromatographed on silica gel using ethyl acetate to give the desired pyrazole (435 mg) as a solid: Anal. calc'd for $C_{18}H_{19}N_3O_3S$: C, 60.49; H, 5.36; N, 11.75. Found: C, 60.22; H, 5.63; N, 11.54.

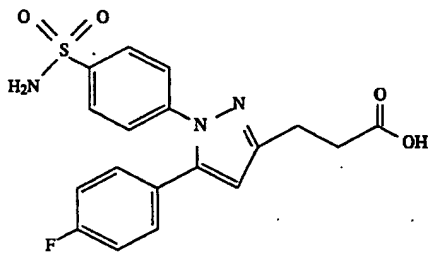
EXAMPLE 25



4-[5-(4-Fluorophenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide

Following the procedure of Example 24, but substituting 4-fluoroacetophenone for acetophenone afforded 4-[5-(4-fluorophenyl)-3-(3-hydroxypropyl)-1H-pyrazol- 1-yl]benzenesulfonamide. Anal. calc'd for $C_{18}H_{18}N_3O_3SF$—0.25 H_2O: C, 56.90; H, 4.91; N, 11.05. Found: C, 56.80; H, 4.67; N, 11.02.

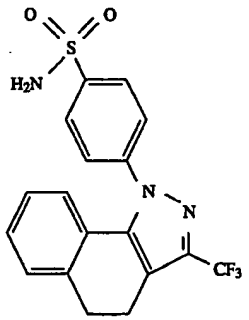
EXAMPLE 26



4-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole]-3-propanoic acid

Jones reagent (0.64 mL of a 2.67M solution) was added dropwise to a solution of 4-[5-(4-fluorophenyl)-3 -(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide from Example 25 (295 mg, 0.78 mmol) in acetone (8 mL). The mixture was stirred at 25° C. for 2 hours. The solution was filtered and the filtrate concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water (3×). The organic solution was dried over $MgSO_4$ and concentrated. The residual oil was crystallized from ether/hexane to give the desired acid. (149 mg, mp 180°–82° C.) Anal. calc'd for $C_{18}H_{16}N_3O_4SF$: C, 55.52; H, 4.14; N, 10.79. Found: C, 55.47; H, 4.22; N, 10.50.

EXAMPLE 27



4,5-Dihydro-4-[3-trifluoromethyl]-1H-benz[g]indazol-1-yl]benzenesulfonamide

Step 1: Preparation of 3-trifluoroacetyl-1-tetralone

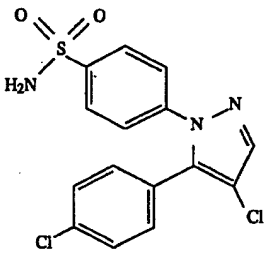
A 250 mL one necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and provisions for magnetic stirring was charged with ethyl trifluoroacetate (28.4 g, 0.2 mol) and 75 mL of ether. To this solution was added 48 mL of 25% sodium methoxide in methanol (0.21 mol). A solution of 1-tetralone (29.2 g, 0.2 mol) in 50 mL of ether was then added over about 5 min. The reaction mixture was then stirred at room temperature for 14 h and then was diluted with 100 mL of 3N HCl. The phases were separated and the organic layer washed with 3N HCl, brine, dried over anhyd. $MgSO_4$, filtered and concentrated in vacuo. The residue was then taken up in 70 mL of boiling ethanol/water and allowed to cool to room temperature whereupon crystals of 2 -trifluoroacetyl-1-tetralone formed which were isolated by filtration and air dried to give 32 g, 81% of pure product

with mp 48°–49° C. ^{1}H NMR $CDCl_3$ δ2.8 (m, 2H), 2.9 (m, 2H), 7.2 (d, j=3.0 Hz, 1H), 7.36 (m, 1H), 7.50 (m, 1H), 7.98 (m, 1H); ^{19} F NMR $CDCl_3$ δ72.0. EI GC-MS M+=242.

Step 2: Preparation of 4,5-dihydro-4-[3-(trifluoromethyl)-1H-benz[g]indazol-1 -yl]benzenesulfonamide

A 100 mL one necked round bottomed flask equipped with reflux condenser nitrogen inlet and provisions for magnetic stirring was charged with 2 -trifluoroacetyl-1-tetralone (1.21 g, 5.0 mmol), 4 -sulfonamido phenylhydrazine hydrochloride (1.12 g, 5.0 mmol) and 25 mL of absolute ethanol. The solution was then warmed to reflux for 15 h and then concentrated in vacuo. The residue was dissolved in ethyl acetate and then washed with water, brine, dried over anhyd. $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and isooctane to give g, 71% of pure product with mp 257°–258° C. ^{1}H NMR ($CDCl_3$/CD_3OD, 4:1) δ2.7 (m, 2H), 2.9 (m, 2H), 6.6 (m, 1H), 6.9 (m, 1H), 7.1 (m, 1H), 7.16 (m, 1H), 7.53 (m, 2H), 7.92 (m, 2H); ^{19} F NMR $CDCl_3$ δ62.5. FAB-MS M+H=394.

EXAMPLE 28



4-[5-(4-Chlorophenyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 5-(4-chlorophenyl)-3 -ketopropionaldehyde

A 4-necked round-bottomed flask equipped with mechanical stirrer, nitrogen inlet, reflux condenser, constant pressure addition funnel and thermometer was charged with 4-chloroacetophenone (77.0 g, 0.5 mol), ethyl formate (40.8 g, 0.55 mol) and 800 mL of ether. The stirrer was started and the solution treated with a solution of 25% sodium methoxide in methanol (123 g, 0.55 mol) from the addition funnel over about 0.5 hour. A heavy white precipitate formed as the sodium methoxide was added. The reaction was stirred at room temperature for 5 hours and was then diluted with an additional 800 mL of ether the precipitate was isolated on a Buchner funnel and washed with thoroughly with ether. The precipitate was dried in vacuo and then placed in a large Erlenmeyer flask and acidified with 3N HCl and then extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a thick orange oil, 60.9 g, 67% of 3-(4-chlorophenyl)-3 -ketopropionaldehyde, IR (neat) 1585 cm^{-1}.

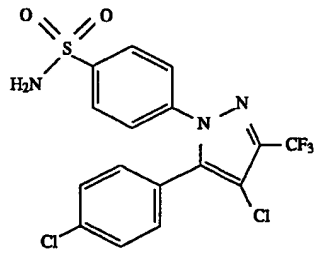
Step 2. Preparation of 4-[5-(4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide

A 250 mL one-necked round-bottomed flask equipped with reflux condenser, nitrogen inlet and provisions for magnetic stirring was charged with 3-(4 -chlorophenyl)-3-ketopropionaldehyde (18.3 g, 0.1 mol), 4 -sulfonamidophenylhydrazine hydrochloride (11.2 g, 0.05 mol) and 100 mL of absolute ethanol. The solution was heated to reflux for 15 hour and then diluted with 100 mL of water and allowed to stand whereupon a white solid formed that was isolated by filtration on a Buchner funnel and air dried to provide 12.6 g, 76% of 4-[5-(4 -chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide, mp 185°–187° C. ^{1}H nmr ($CDCl_3$/300 MHz) 7.89(d, J=8.7 Hz, 2H), 7.76(d, J=1.8 Hz, 1H), 7.43(d, J=8.7 Hz, 2H), 7.34(d, J=8.7 Hz, 2H), 7.17(d, J=8.7 Hz, 2H), 6.53(d, J=1.8 Hz, 1H), 4.93(brs, 2H), mass spectrum MH^+= 334.

Step 3. Preparation of 4-[5-(4-Chlorophenyl)-4 -chloro-1H-pyrazol-1-yl]benzenesulfonamide

A 100 mL three-necked round-bottomed flask equipped with reflux condenser, gas dispersion tube and provisions for magnetic stirring was charged with 4-[5 -(4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide (500 mg, 1.2 mmol) and 50 mL of glacial acetic acid. The solution was stirred at room temperature and treated with a stream of chlorine gas for a period of 15 minutes. The solution was then stirred at room temperature for 1.25 hours and then diluted with 100 mL of water. The solution was then extracted three times with ether and the combined ethereal phase washed with brine, dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to give a white solid that was recrystallized from ether/petroleum ether to provide 400 mg, 75% of 4-[5-(4 -chlorophenyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide, ^{1}H nmr ($CDCl_3$/300 MHz) 8.06 (s, 1H), 7.81(d, J=8.4 Hz, 2H), 7.53(d, j=8.4 Hz, 2H), 7.43(brs, 2H), 7.42(d, J=8.4 Hz, 2H), 7.32(d, J=8.4 Hz, 2H).

EXAMPLE 29

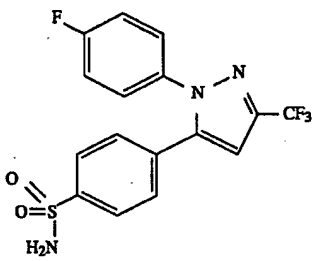


4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide

A 100 mL three-necked round-bottomed flask equipped with reflux condenser, gas dispersion tube and provisions for magnetic stirring was charged with 4-[5 -(4-chlorophenyl)-3-trifluoromethyl-1H-pyrazol-1 -yl]benzenesulfonamide (500 mg, 1.2 mmol) and 50 mL of glacial acetic acid. The solution was stirred at room temperature and treated with a stream of chlorine gas for a period of 15 minutes. The solution was then stirred at room temperature for 1.25 hours and then diluted with 100 mL of water. The solution was

then extracted three times with ether and the combined ethereal phase washed with brine, dried over anhyd. $MGSO_4$, filtered, and concentrated in vacuo to give a while solid that was recrystallized from ether/petroleum ether to provide 390 mg, 75% of 4-[5-(4-chlorophenyl)-4-chloro-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide, mp 180°–182° C. ^1H nmr ($CDCl_3$/300 MHz) 7.97(d, J=6.6 Hz, 2H), 7.49(d, J=6.3 Hz, 2H), 7.45(d, J=6.3 Hz, 2H), 7.25(d, J=6.6 Hz, 2H), 5.78(brs, 2H).

EXAMPLE 30



4-[1-(4-Fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide

Step 1: Preparation of N,N-bis(4-methoxybenzyl)-4-(aminosulfonyl)acetophenone

To a solution of 4-(aminosulfonyl)acetophenone (2.0 g, 9.0 mmol) in dimethylsulfoxide (25 mL) was added NaOH (450 mg, 19.0 mmol). The reaction mixture was stirred for 45 minutes and then 4-methoxybenzyl bromide (3.5 g, 19.0 mmol) in dimethylsulfoxide (5 mL) was added via canula. The mixture was stirred at room temperature for 24 hours and partitioned between ethyl acetate and pH 7 buffer. The aqueous solution was extracted with ethyl acetate. The organic solution was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (2:1 hexane:ethyl acetate) to give the desired product (815 mg, 21%).

Step 2: Preparation of N,N-bis(4-methoxybenzyl)-4-[1-(4-fluorophenyl)-3-trifluoromethyl-1H-pyrazol-5-yl]benzenesulfonamide

Ethyl trifluoroacetate was placed in a 500 mL three-necked round bottom flask, and dissolved in methyl tert-butyl ether (75 mL). To the stirred solution was added 25 weight % sodium methoxide via an addition funnel over a 2 minute period. Next the protected acetophenone from step 1 was dissolved in methyl tert-butyl ether (20 mL), and added to the reaction dropwise over 5 minutes. After stirring overnight (15.75 hours), 3N HCl (70 mL) was added. The organic layer was collected, washed with brine (75 mL), dried over $HgSO_4$, filtered, and concentrated in vacuo. The solid was recrystallized from iso-octane to give the dione. 4-Fluorophenyl hydrazine hydrochloride was added to a stirred solution of the dione in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate and washed with water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo to give a light brown solid which was recrystallized from ethyl acetate and iso-octane to give the protected pyrazole.

Step 3: Preparation of 4-[1-(4-fluorophenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide

To a solution of the protected pyrazole (50 mg, 0.08 mmol) in acetonitrile (1 mL) and water (0.3 mL) was added ceric ammonium nitrate (360 mg, 0.65 mmol). The reaction solution was kept at room temperature for 16 hours. The solution was poured into water (15 mL) and extracted with ethyl acetate (2×25 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (2:1 hexane:ethyl acetate) to give the desired product (13 mg, 42%). ^1H NMR (CD_3OD) 7.88 (d,2H), 7.46 (d, 2H), 7.39 (dd, 2H), 7.21 (t, 2H), 7.06 (s, 1H).

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in *Non-Steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). Results are shown in Table I.

Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table I.

TABLE I

	RAT PAW EDEMA % Inhibition @ 10 mg/kg body weight	ANALGESIA % Inhibition @ 20 mg/kg body weight
Examples		
1	44	51
1f	42*	
2	39	46

*Assay performed at 20 mg/kg body weight

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

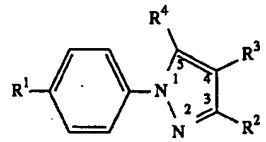
The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably from about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula I



(I)

wherein R^1 is sulfamyl;

wherein R^2 is haloalkyl;

wherein R^3 is selected from hydrido, and alkyl; and

wherein R^4 is selected from aryl, cycloalkyl, and cycloalkenyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino;

or a pharmaceutically-acceptable salt thereof.

2. Compound of claim 1 wherein R^2 is lower haloalkyl;

wherein R^3 is hydrido; and

wherein R^4 is selected from aryl, cycloalkyl, and cycloalkenyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, amido, lower N-monoalkylamido, N-monoarylamido, lower N,N-dialkylamido, lower N-alkyl-N-arylamido, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, sulfamyl, lower N-alkylsulfamyl, amino, lower N-alkylamino, lower N,N-dialkylamino, heterocyclic, nitro and acylamino;

or a pharmaceutically-acceptable salt thereof.

3. Compound of claim 2 wherein R^2 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, and dichloropropyl;

wherein R^3 is hydrido; and

wherein R^4 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2 -cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, cyano, carboxyl, amido, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tertbutoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, N-methylamido, N-ethylamido, N-isopropylamido, N-propylamido,

N-butylamido, N-isobutylamido, N-tert-butylamido, N-pentylamido, N-cyclohexylamido, N-cyclopentylamido, N,N-dimethylamido, N-methyl-N-ethylamido, pyrrolidinoamido, piperidinoamido, N-phenylamido, N-(3-fluorophenyl)amido, N-(4-methylphenyl)amido, N-(3-chlorophenyl)amido, N-(4-methoxyphenyl)amido, 2-pyridylamido, N-methyl-N-phenylamido, N-methyl-N-pyridylamido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, trifluoromethoxy, hydroxymethyl, hydroxymethyl, hydroxypropyl, sulfamyl, methylsulfamyl, amino, nitro, methylamino, dimethylamino, formylamino, acetamino, trifluoroacetamino and morpholino;

or a pharmaceutically-acceptable salt thereof.

4. Compound of claim **1** wherein R^1 is sulfamyl; wherein R^2 is lower haloalkyl; wherein R^3 is lower alkyl; and wherein R^4 is selected from aryl, cycloalkyl, and cycloalkenyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, amido, lower N-monoalkylamido, N-monoarylamido, lower N,N-dialkylamido, lower N-alkyl-N-arylamido, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, sulfamyl, lower N-alkylsulfamyl, amino, lower N-alkylamino, lower N,N-dialkylamino, heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

5. Compound of claim **4**

wherein R^2 is lower haloalkyl; wherein R^3 is lower alkyl; and wherein R^4 is aryl optionally substituted at a substitutable position with halo; or a pharmaceutically-acceptable salt thereof.

6. Compound of claim **5**

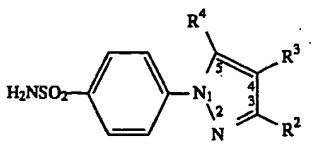
wherein R^2 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl;

wherein R^3 is selected from methyl, ethyl, propyl, isopropyl, and butyl; and

wherein R^4 is phenyl optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro and bromo;

or a pharmaceutically-acceptable salt thereof.

7. A compound of Formula II



(II)

wherein R^2 is lower haloalkyl;

wherein R^3 is hydrido; and

wherein R^4 is selected from aryl, cycloalkyl, and cycloalkenyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfonyl, cyano, nitro, lower haloalkyl, lower alkyl, hydrido, lower alkoxy, lower haloalkoxy, sulfamyl, heterocyclic and amino;

or a pharmaceutically-acceptable salt thereof.

8. Compound of claim **7**

wherein R^2 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl; wherein R^3 is hydrido; and wherein R^4 is selected from phenyl, biphenyl, cyclohexyl, and cyclohexenyl; and wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from chloro, bromo, fluoro, methylthio, methylsulfonyl, morpholinyl, amino, nitro, methyl, ethyl, propyl, isopropyl, butyl, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl;

or a pharmaceutically-acceptable salt thereof.

9. Compound of claim **8** where the compound is 4 -[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

10. Compound of claim **8** where the compound is 4-[5-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

11. Compound of claim **3** selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-[4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-[4-(trifluoromethoxy)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-[4(methylthio)phenyl]-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2,6-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-biphenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;

4-[5-[4-(morpholino)phenyl]-3-(difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(1-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-[4-(trifluoromethyl)phenyl]-3-(difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(fluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(chloromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(dichloromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(dichlorofluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(3,5-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2,4,6-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2,6-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2,4,6-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dimethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(3,4-methylenedioxyphenyl)-3-trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2-fluoro-4-methoxyphenyl)-3-trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-fluoro-2-methoxyphenyl)-3-trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2-chloro-4-methoxyphenyl)-3-trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-chloro-2-methoxyphenyl)-3-trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2-methythiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-methythiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methythiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(3-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(2-fluoro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-fluoro-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2-chloro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-chloro-2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(3,4-dihydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-biphenyl-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-ethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-isopropylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(6-methoxy-2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;

4-[5-[4-(N-ethylamino)phenyl)]-3-trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-[4-(N,N-dimethylamino)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-[4-(N-formylamino)phenyl]-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-[4-(N-acetamino)phenyl]-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-[4-(N-methylsulfonamido)phenyl]-3 -(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-hydroxymethylphenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(cyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;

4-[5-(cyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;

4-[5-(cycloheptyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(trifluoroethyl)-1H-pyrazol-1 -yl]benzenesulfonamide; and

4-[5-(1-cyclopentenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide.

12. Compound of claim **6** selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-4-(methyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-4-(n-propyl)-1H-pyrazol-1-yl]benzenesulfonamide; and

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-4-(methyl)-1H-pyrazol-1-yl]benzenesulfonamide.

13. Compound of claim **8** selected from compounds, and their pharmaceutically-acceptable salts, of the group consisting of

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-[4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-[4-(trifluoromethoxy)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methylphenyl)-3-(trifluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylthiophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(2,6-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-biphenyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl] benzenesulfonamide;

4-[5-(4-(morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1 -yl]benzenesulfonamide;

4-[5-(4-[trifluoromethyl]phenyl)-3-(difluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide;

4-[5-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide; and

4-[5-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol- 1-yl]benzenesulfonamide.

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